Organocatalytic Synthesis of Six Membered Nitrogen Heterocycles and Related Alkaloids

THESIS

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DOCTOR OF PHILOSOPHY

by

Panduga Ramaraju

Under the supervision of

Dr. Indresh Kumar

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE

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2016

Dedicated

to My Family

and

Teachers

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
PILANI (RAJASTHAN)

CERTIFICATE

This is to certify that the thesis entitled "**Organocatalytic Synthesis of Six Membered Nitrogen Heterocycles and Related Alkaloids"** and submitted by **Mr. Panduga Ramaraju** ID No **2012PHXF021** for award of Ph.D. Degree of the Institute embodies the original work done by him under my supervision.

Signature in full of the Supervisor:

Name: **Dr. INDRESH KUMAR**

Designation: **Assistant Professor**

Date:

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P. Ramaraju

Abstract

Nitrogen containing heterocyclic compounds have broad applications in the multidisciplinary fields. The work mentioned in the thesis entitled "**Organocatalytic Synthesis of Six-membered Nitrogen Heterocycles and Related Alkaloids**" deals with the synthesis of some selected six-membered nitrogen heterocycles such as substituted piperidines, 1,2-Dihydropyridines, 1,2,5,6-tetrahydropyridines, and isoquinuclidines in asymmetric fashion. The main strategy involves utilization of linear dialdehydes such as glutaraldehyde which acts as 1,4-carbon *donor-acceptor* precursor with various *N*-PMP-aldimines as another counterpart by employing the multi-bond forming procedures like one-pot operation, tandem sequences, multi-component reactions by utilizing the concept of covalent amino organocatalyzed direct Mannich reactions. This thesis is divided into six chapters.

The first chapter of the thesis describes a brief discussion of organocatalysis, in particular amine catalysis as green protocol in synthetic chemistry. The extensive literature survey on amine-catalyzed direct Mannich reactions, its progress in the development of synthetic methods for complex scaffolds from the past decade along with its significant role in the development of diverse synthetic methods is described. The importance of nitrogen heterocycles and the exploration of the glutaraldehyde as 1,4-carbon *donor-acceptor* is described for the synthesis of biologically important complex scaffolds through the organocatalytic intermolecular transformation methods. The chapter also covers the contribution of the amine catalysis as a green process in synthetic chemistry from the past decade.

The second chapter describes a rational design and synthesis of novel enantioselective piperidines. This approach involves proline catalyzed [4+2] annulations between glutaraldehyde and a wide variety of Ar/HetAr-PMP-imines as a one pot sequence producing 2,3-disubstituted piperidines in good yields (61–90 %) and high enantioselectivity (> 99 % ee). The utility of the developed methodology was further shown by synthesizing functionalized (−)-anabasin. Gram-scale reactions were also performed to demonstrate the potency of optimized procedure for the scale-up process.

The third chapter discloses the enantioselective synthesis of 1,2-dihydro pyridines (DHPs) *via* formal [4+2] cycloaddition. The reactions proceeds through proline catalyzed direct Mannich reaction/cyclization between readily available glutaraldehyde and easily accessible N-PMP aldimines followed by site selective IBX oxidation sequence in one pot with good yields (66–87 %) and excellent enantioselectivity (> 99:1 er). Further application of this method was shown by synthesizing chiral fused polycyclic *N*-heterocyclic compounds.

The Fourth chapter describes a multicomponent enantioselective synthesis of 1,2,5,6-tetrahydropyridines (THPs) from glutaraldehyde, Ar/HetAr-aldehydes and p-methoxyaniline through [4+2] annulation/oxidation/reduction sequence in one pot operation. The reaction proceeded well with good yields (53–80 %) and high enantiomeric ratios (up to > 98:2 er). The practical utility of these molecules was also shown by synthesizing biologically important N-hetocycles such as imino-sugar, nipecotic acid derivatives, guvacine analogue, and structural analog of 2-Epi-CP-99 994.

The fifth chapter describes the two pot sequence for enantio- and diastereoselective synthesis of isoquinuclidines. This methodology involves proline catalyzed enantioselective [4+2] annulation between glutaraldehyde and aldimines, followed diastereoselective Diels-Alder (D-A) reaction of intermediate DHP alcohols with *N*-Phenylmalimide to produce isoquinuclidines in good yields (41–81 %) and with diastereo- (up to 25:1 dr), and enantioselectivity (97:3 er). These isoquinuclidines are synthetically useful scaffolds for synthesizing oseltamivir drug analogues and related complex natural products and synthetic compounds such as *iboga*-alkaloids.

The sixth chapter summarizes the overall thesis work. The future scope of the research work undertaken is also highlighted in this chapter.

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LIST OF ABBREVIATIONS / SYMBOLS

Abbreviation/Symbol	Description
AcOH	Acetic acid
α	Alpha
[α]	specific rotation
β	Beta
γ	Gamma
δ	Chemical shift
Å	Angstrom
Ac	Acetyl
Aq	Aqueous
ACN	Acetonitrile
Ar	Aryl
Bu	Butyl
t-BuOK	Potassium *tert*-butoxide
Calcd.	Calculated
°C	Degree centigrade
^{13}CNMR	Carbon-13 nuclear magnetic resonance
Cat.	Catalyst
CAN	Ceric ammonium nitrate
$CDCl_3$	Deuterated chloroform
Conc	Concentration
COSY	Correlation Spectroscopy (NMR)
d	Doublet
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
dd	Doublet of doublet
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
DMSO	Dimethy sulphoxide
DCE	Dichloroethane
DCM	Dichloromethane

LIST OF ABBREVIATIONS / SYMBOLS

DMA	*N*,*N*-Dimethylacetamide
DMAD	Dimethyl acetylene dicarboxylate
DMF	*N*,*N*-Dimethylformamide
ESI	Electron Spray Ionization (MS)
EtOAc	Ethyl acetate
Equiv	Equivalent
E	Electrophile
g	Gram
Fe	Iron
h	Hours
HRMS	High Resolution Mass Spectra
HSQC	Heteronuclear Single Quantum Correlation
IBX	2-Iodoxybenzoic acid
IR	Infrared
Hz	Hertz
hr	Hour
i	*iso*
J	Coupling constant
Lit.	Literature
MCR	Multi component reaction
Me	Methyl
MS	Mass spectrometry
M.P	Melting point
m	Multiplet
mg	Milligram
MHz	Mega hertz
min	Minutes
mL	Milliliter
mmol	Millimole
MW	Microwave

LIST OF ABBREVIATIONS / SYMBOLS

N_2	Nitrogen gas
Nu	Nucleophile
NaH	Sodium hydride
NaOH	Sodium hydroxide
^{I}HNMR	Proton Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect (NMR)
NOESY	Nuclear Overhauser Effect Spectroscopy (NMR)
O_2	Oxygen gas
PEG	Polyethylene glycol
Ph	Phenyl
ppm	Parts per million
%	Percentage
psi	Per square inch
p-TsOH	*p*-Toluenesulfonic acid
PMP	*p*-methoxyphenyl
rt	Room temperature
s	Singlet
NBS	*N*-bromosuccinimide
$NaHCO_3$	Sodium hydrogencarbonate
t	Triplet
t	Tertiary
TBAB	Tetrabutylammonium bromide
Ts	Tosyl
Tert-	Tertiary
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMS	Tetramethylsilane
σ	Sigma
*	Chiral

Chapter-1

Introduction to Amine-Catalyzed Direct Mannich reactions and Utilization of Glutaraldehyde in Cascade Reactions

1.1 Organocatalysis

The acceleration of chemical reactions through the addition of a sub-stoichiometric quantity of an organic compound is called organocatalysis. The interest in this field has increased spectacularly in the last few years as a result of both the novelty of the concept and, more importantly, the fact that the efficiency and selectivity of many organocatalytic reactions meet the standards of established 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 to the scientific community in 2000 by MacMillan, in order to describe the field of organic synthesis that utilized low molecular weight simple organic molecules to catalyze given transformations.[3- 4]

The organocatalyst could be achiral or chiral and may contain C, H, N, S, and P. During the last decade, organocatalysis has been included among the most important and a successful concept in asymmetric catalysis and it has been used for the enantioselective construction of C-C, C-N, C-O, C-S, C-P and C-halide bonds.[5-10] Organocatalysis has several advantages not only because of its synthetic range, but also 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. Nowadays, organocatalysis is one of the hot research topics in advanced organic chemistry. It is a novel synthetic philosophy and mostly an alternative to the prevalent transition metal catalysis. Organocatalysts are often based on nontoxic organic compounds originating from biological materials. Moreover, nature provides us with an array of enantiopure organic compounds from which to develop organic catalysts. These include α-amino acids, α-hydroxy acids, nucleic acids, and carbohydrates. Recently the use of small chiral organic molecules as catalysts with the associated advantages of their easy availability and of carrying out the asymmetric transformation in a metal free environment and under mild and simple reaction conditions has experienced an impressive growth in the emerging field of chemistry from last more than one decade.

The renewal of proline-catalyzed transformations in early 2000 by 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 Baylis-Hilman, Mannich, Michael additions, Henry, Aldol, Stetter, Knoevenagel reactions,

phase-transfer catalysis. Further cycloaddition, substitution, elimination and rearrangement reactions in all types of synthetic processes fall in this category which are having significant contributions in 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 chapter is on organocatalytic direct Mannich reactions.

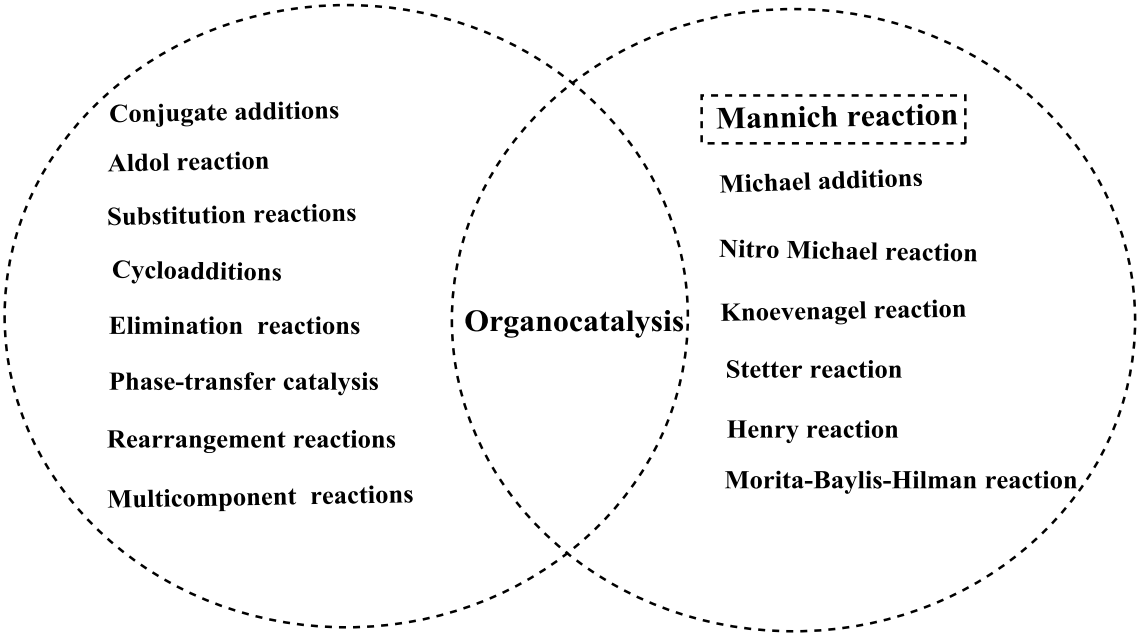


Figure 1.1 Different types of organocatalytic reactions

Most of the organocatalysts are air and moisture stable thus making them more practical for use in synthetic laboratory. They are easy to handle even on a large scale and relatively less toxic compared to transition metals. Moreover, frequently the reactions are conducted under mild conditions and high concentrations thus escaping the use of large amounts of solvents and minimizing waste.[13] Organocatalysts are readily available, environmental friendly and stable under aerobic and non-aerobic conditions, which results in better reproducibility and operational simplicity than metal-catalyzed procedures.[14] During the last decade, organocatalysis has been one of the most rapidly growing and competitive field in asymmetric catalysis and developed as a third pillar beside metal and biocatalysis.[15] In addition to these characteristics, organocatalysts are tolerant of numerous functional groups, seek to reduce energy consumption, and avoid time-consuming and protecting group manipulations for carrying out such type of chemical transformations.

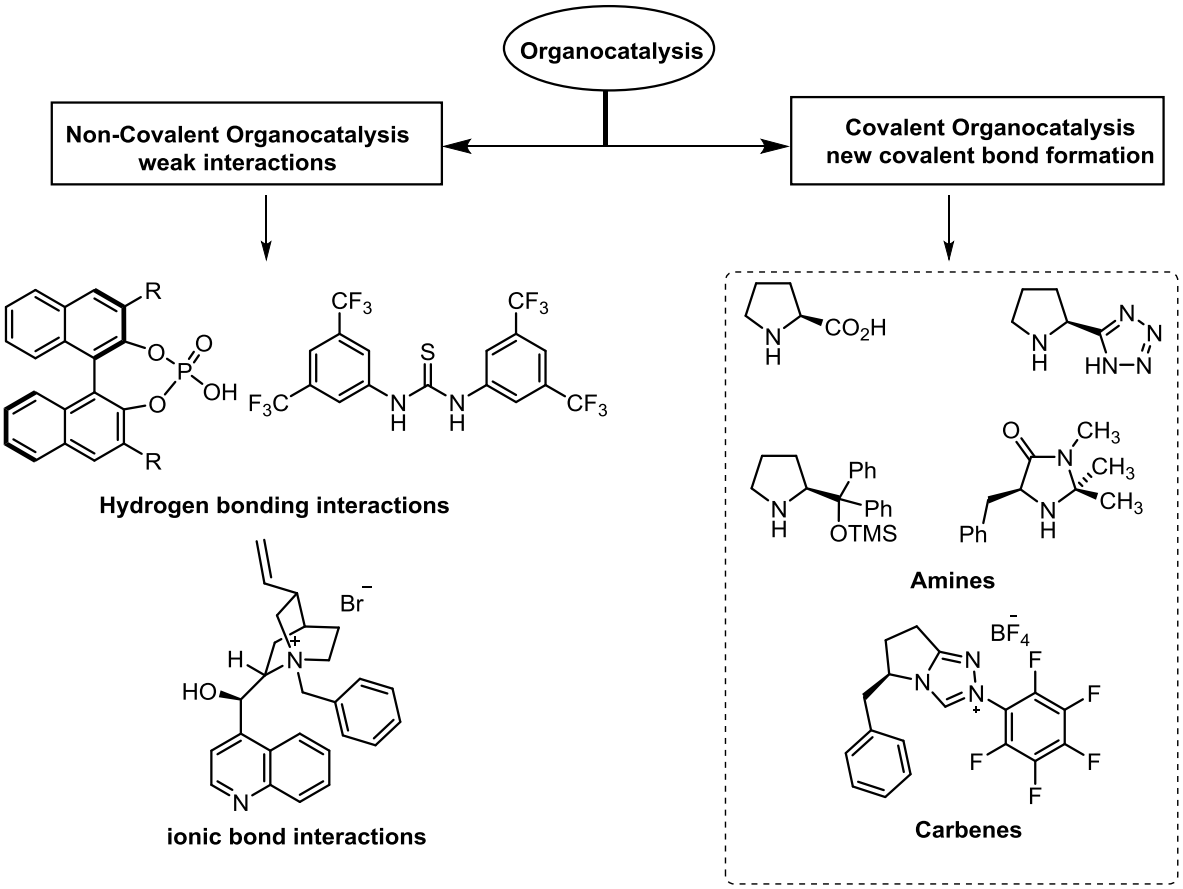


Figure 1.2 General classifications of amine-catalysis

Various types of organocatalysts, such as amino acids, peptides, Cinchona alkaloids, chiral thioureas, 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 electrophile and the nucleophile), in addition to create a chiral environment responsible for setting the chirality in the product. Organocatalysts can be classified into two main categories such as covalent and non-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, aminocatalyst [16] and carbene catalysts [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

Amines can activate carbonyl compounds toward nucleophilic addition was previously recognized in the late 1800's 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 substrate through 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.

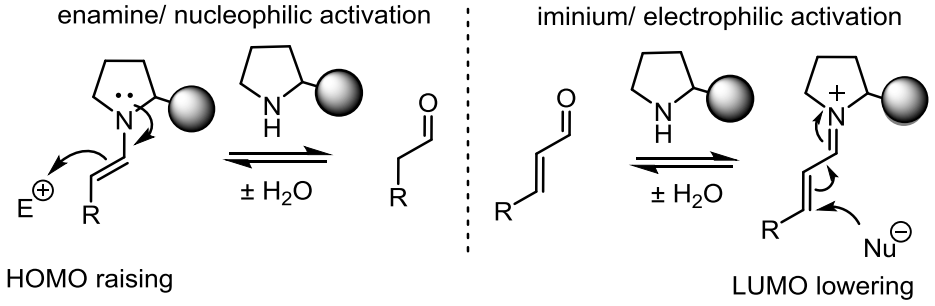


Figure 1.3 Iminium ion and enamine activation modes of aminocatalysis

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 carbonyl compound through enamine-intermediate. (**Figure 1.4**)

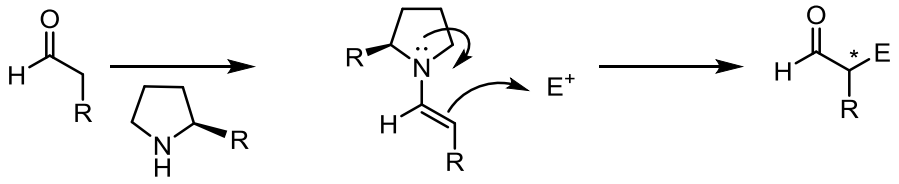
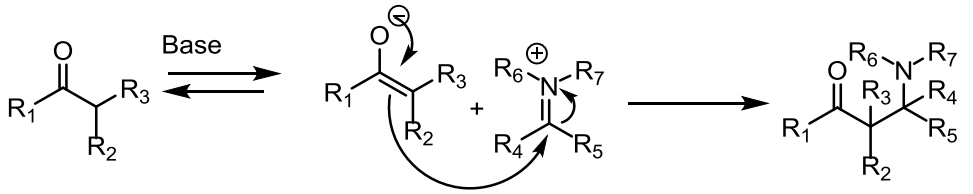


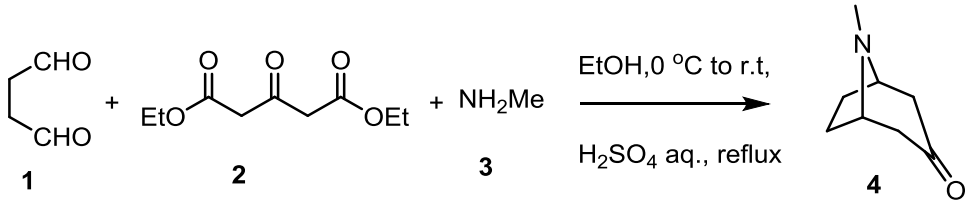
Figure 1.4 Covalent mode of activation of substrates through enamine intermediate catalysis

1.3 Mannich Reaction

Mannich reaction is used to convert an enolizable carbonyl compounds with primary or secondary amine in presence of base to produce β-amino carbonyl compounds. This reaction is also called as amino alkylation. Mannich reaction is named after a German Chemist Carl Ulrich Franz Mannich in 1912. A general mechanistic aspect is shown in the following **Scheme 1.1** [50]



Scheme 1.1 General representative Mannich reaction

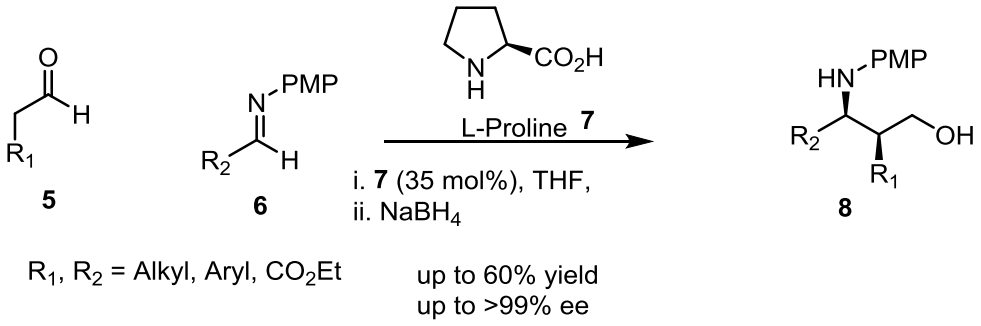


Scheme 1.2 Important utilization of Mannich reaction for the synthesis of tropinone

This is an important reaction because of the incorporation of the nitrogen atom in to 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 acetone dicarboxylate **2**, and methylamine (**3**) gave the desired product after two fold decarboxylation in a synthesis that is nowadays recognized as a classic in linear synthesis (**Scheme 1.2**).

1.4 Development of amino-catalytic asymmetric 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 described the first the L-proline **7** as an organocatalyzed Mannich reaction.[69,70] This landmark discovery stimulated the rapid development of many asymmetric organocatalytic Mannich reactions.



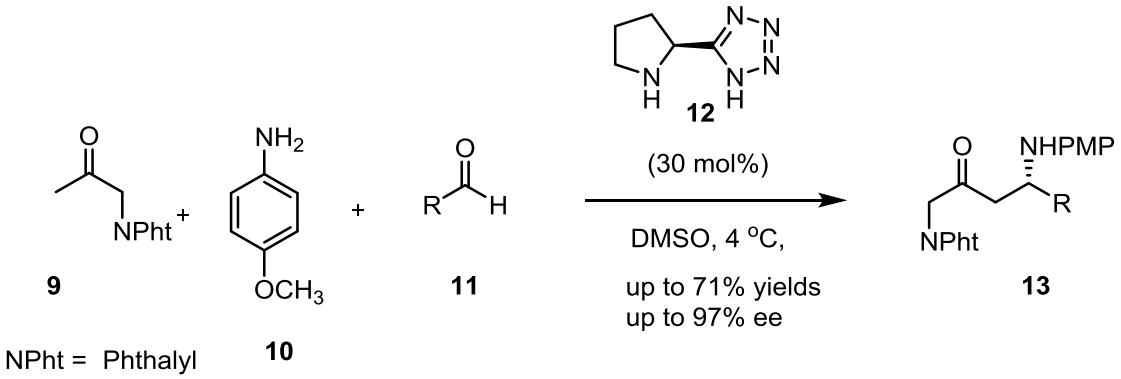
Scheme 1.3 First organocatalytic asymmetric Mannich reaction

The typical organocatalytic approach to asymmetric Mannich reaction is based on enamine activation of carbonyl compounds using secondary amine organocatalysts.[27] In this chapter we describe direct asymmetric Mannich reactions through covalent mode of activation by amine catalysis. The asymmetric organocatalytic Mannich reaction is now considered as 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]

Organocatalytic Mannich reactions can be carried out by either as three-component one-pot reactions, or 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 regeneration of the amine catalyst through hydrolysis. The products are β-amino aldehydes or β-amino ketones, which are substituted at the α-position.[75] Among a wide variety of organocatalysts that have been used in the asymmetric Mannich reaction, the most widely used catalysts are proline and its derivatives.

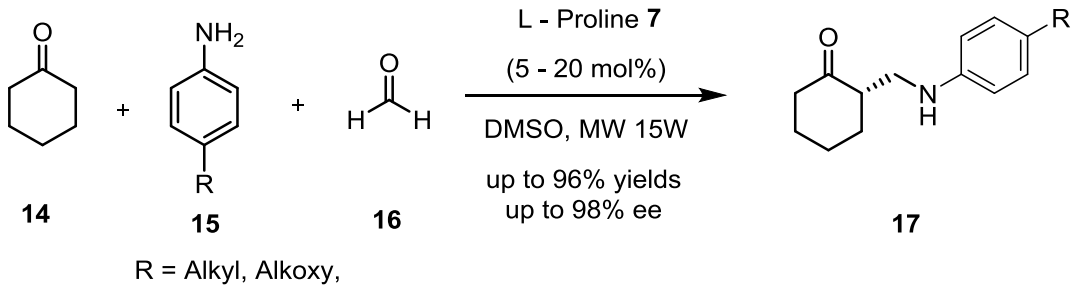
1.5 Asymmetric Mannich reaction

After the initial development of asymmetric Mannich reaction by List, a huge number of protocols were developed by different researchers around the globe which collectively reviewed by List group.[30] The organocatalytic asymmetric three-component Mannich reaction has significantly expanded the synthetic scope and value of this transformation. Mannich reactions of protected amino ketones **9**, *p*-anisidine **10**, and aldehydes **11** in the presence of pyrrolidine based tetrazole catalyst **12** have been explored by C. F. Barbas III and co-workers.[76] These reactions provide highly regio-, and enantioselectivity, thus an efficient methods for the asymmetric synthesis of 1,4-diamines **13** from phthalimido ketones as shown in **Scheme 1.4**. This represent the first example of highly stereoselective catalytic access to chiral 1,4-diamines **13** using the Mannich reaction.



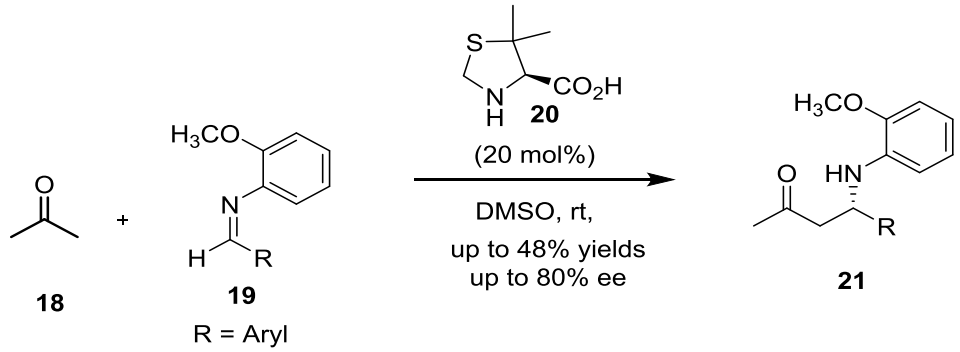
Scheme 1.4 Asymmetric Mannich Reaction for the Synthesis of Protected 1,4-Diamine

C. Bolm and Rodriguez investigated the (*S*)-proline **7** catalyzed enantioselective *R*-aminomethylation between ketone **14**, aqueous formaldehyde **16**, and aniline **15**. By applying microwave irradiation power heating with simultaneous air-cooling, reaction times and catalyst loadings could be reduced. For example, complete consumption of cyclohexanone **14**, formaldehyde **16**, and aniline **15** occurred within 2.5 h in the presence of (*S*)-proline (10 mol %) in DMSO under a microwave power of 15W, giving the corresponding product **17** as shown in **Scheme 1.5**.[77]



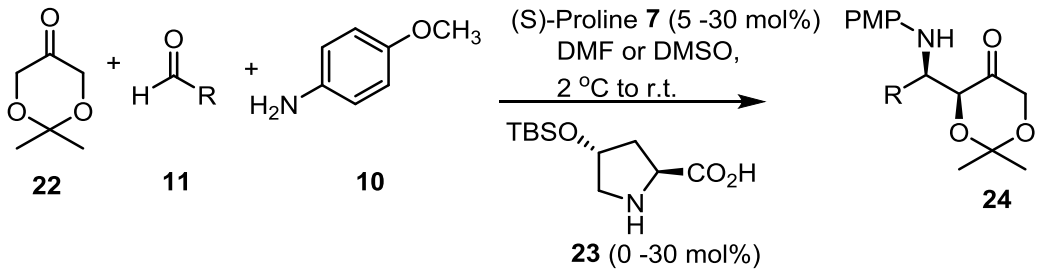
Scheme 1.5 Proline catalyzed Multicomponent asymmetric Mannich reaction

Barbas and co-workers reported (*S*)-5,5-dimethylthiazolidine- 4-carboxylic acid **20** catalyzed asymmetric Mannich reactions of acetone **18** with a variety of preformed imines **19** or in situ generated aldimines derived from *o*-anisidine for the synthesis of corresponding product **21** [78] that is showing the advantage of the Mannich reaction as represented in **Scheme 1.6**.



Scheme 1.6 Organocatalytic asymmetric Mannich reaction with preformed imines

The organocatalytic entry to amino sugars *via* the Mannich reaction has been broadened by the groups of Córdova,[79] Westermann,[80] and Enders[81] with the use of protected dihydroxyacetone **22** (**Scheme 1.7**). The yields and selectivities of the product **24** was high. The group of Westermann used performed imines from aldehyde **11**, and *p*-methoxy aniline **10** while both Córdova and Enders developed three-component reactions. Moreover, Enders reported TBS-protected 4-hydroxyproline **23** to be a superior catalyst due to the better solubility.

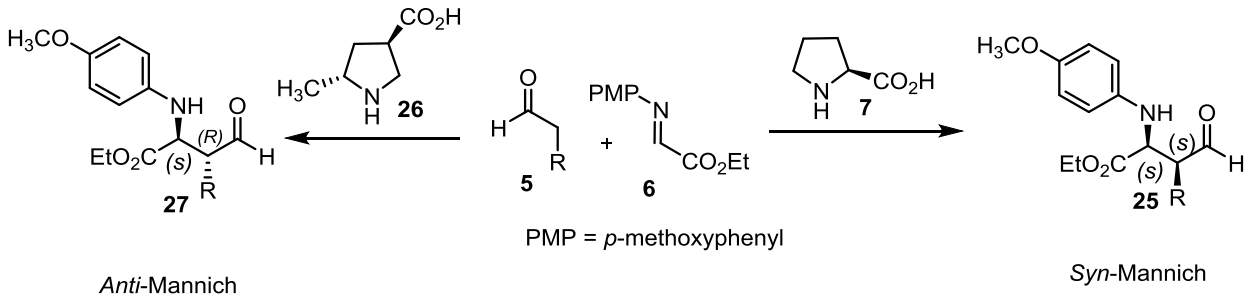


Scheme 1.7 Synthesis of aminoketones through Mannich reaction

The asymmetric Mannich reaction through covalent mode of activation is of two types based on the stereo chemical outcome of the product as shown in the following S**cheme 1.8**.

1.5.1 *Syn*-Mannich reaction

1.5.2 *Anti*-Mannich reaction

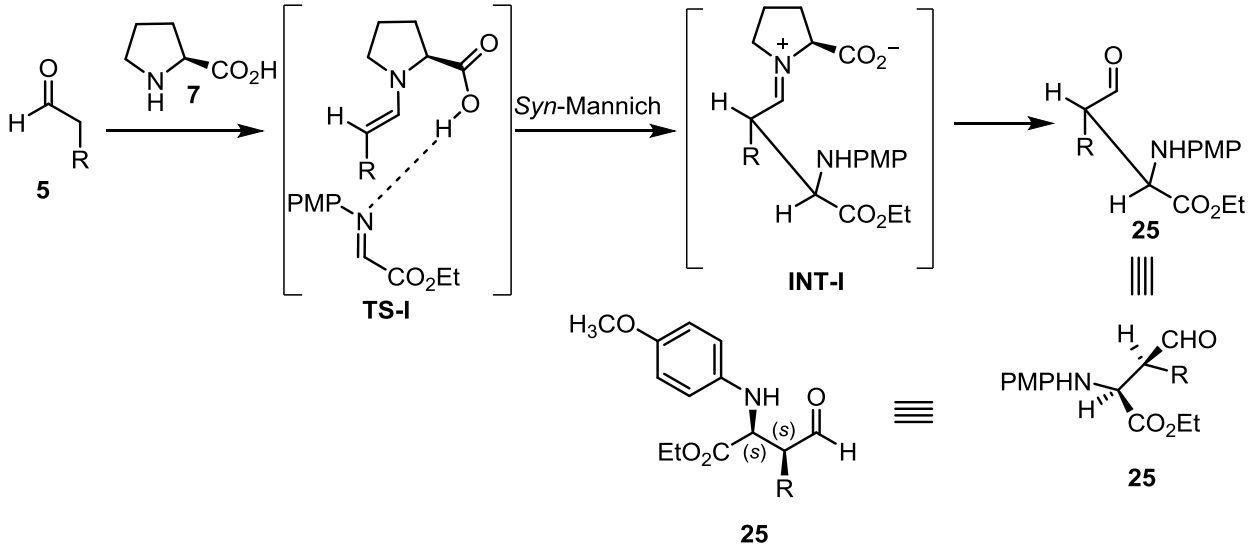


Scheme 1.8 Organocatalytic asymmetric *syn* and *anti* Mannich reactions

The name *syn* or *anti*-Mannich reaction depends on the overall stereochemical outcome of the product through a rationale chiral transition state. If the Mannich product attained the *cis*-chiral centers, then it is called as *syn*-Mannich reaction, and if the product has the *trans*-chiral centers, then the strategy is called as *anti*-Mannich reaction. The following schemes give the clear idea about these two complementary strategies.

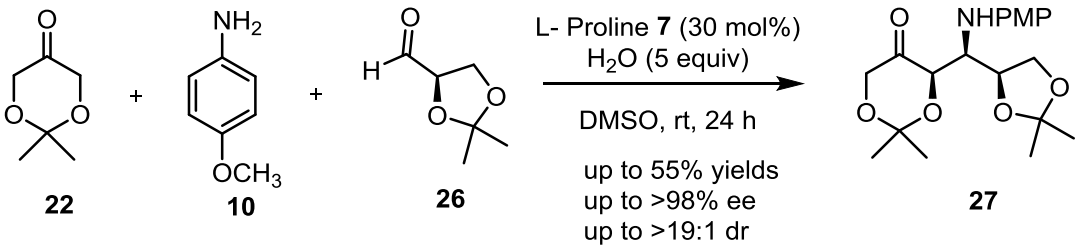
1.5.1 *Syn*-Mannich reaction

Most of the organocatalytic Mannich reactions are proline derived catalytic approaches and several number of asymmetric *syn*-Mannich reactions were explored in the literature.



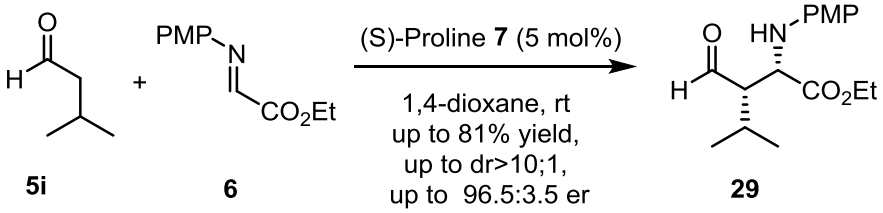
Scheme 1.9 Mechanistic aspect of organocatalytic asymmetric *syn*-Mannich reaction

Córdova and co-workers explored a three-component asymmetric *syn*-Mannich reaction by using protected dihydroxyacetone **22**, *p*-anisidine **10**, and an aldehyde **26** in presence of L-proline **7** as catalyst to afford protected 4-amino-4-deoxy-D-fructose **27** [82] as shown in **Scheme 1.10**.



Scheme 1.10 Asymmetric Mannich reaction for the synthesis of amino sugar derivative

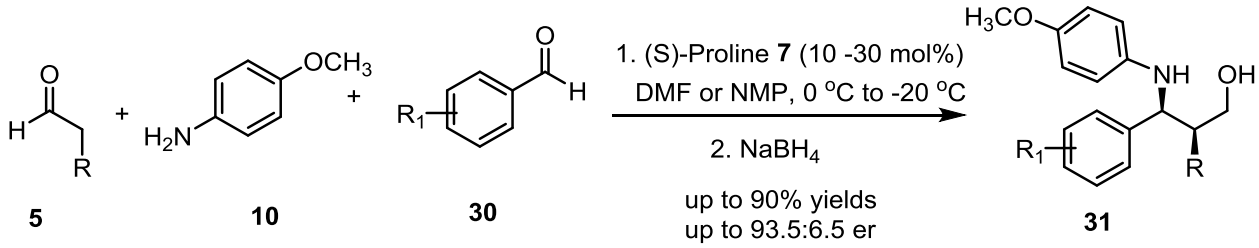
The Barbas group made an important contribution to the development of the proline catalyzed Mannich reaction by introducing aldehydes as donors.[83] Like-wise, *N*-PMP protected α-imino ester **6** was reacted with a small excess of iso-valeraldehyde **5i** (1.5 equiv) to yield protected α-amino-ester **29** (**Scheme 1.11**). The diastereomeric ratio was higher with increased steric bulk on the aldehyde. It was noted that some products epimerized upon purification by column chromatography. Similar results were published by the same group while using preformed α-imino-esters as starting materials.[81] These esters are useful substrates for α-amino acids synthesis.



Scheme 1.11 First use of unmodified aldehydes in the proline-catalyzed Mannich reaction

The development of a three-component, proline-catalyzed cross-Mannich reaction of two unmodified aldehydes and *p*-methoxyaniline **13** was reported independently by the groups of Hayashi,[84] and Córdova.[85] While the two 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 (**31)** (**Scheme 1.12**). A variety of aldehydes **5** 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 below 95:5. In most of the cases, the reactions gave

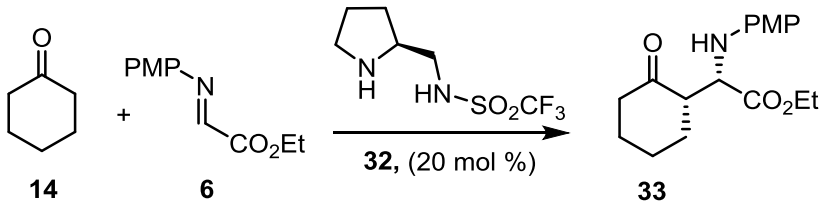
good to high yields (70-90 %). While, the aromatic aldehydes **30** were mostly used as acceptors. Barbas also reported the self-Mannich reaction between two aliphatic aldehydes.[86] The products were generally formed with lower selectivities, with diastereomeric ratios (around 5:1) and enantiomeric ratios (*er*) (90.5:9.5 to 93.5:6.5.). The product **31** was formed with poor *er* (59:41) when *iso*-valeraldehyde **5** was utilized as the sterically bulky aldehyde in this screening process.



Scheme 1.12 Enantioselective three-component cross-Mannich reaction of unmodified aldehydes

It can be seen from the literature reviewed so far that proline has emerged as a catalyst of broad utility for the Mannich reaction. Apart from its high selectivity, easy handling, and non-toxicity, it has the additional advantage of being cheap and available in both enantiomeric forms. However, several researchers have been interested in finding different catalysts. List[69] and Barbas[78] have developed pyrrolidine-derived catalysts for the Mannich reaction between ketones and aldehydes, however proline still remained as the catalyst of choice. Córdova screened acyclic amino acids such as alanine or serine, which also catalyzed the Mannich reaction with good selectivities.[87]

Wang and coworkers disclosed the use of pyrrolidine-sulfonamide **32** as an alternative for the direct Mannich reaction of cyclohexanone **14** with ethylglyoxalate-imine **6** in protic and aprotic solvents with yields varying from 76% to 90% (**Scheme 1.13**).[88] Hence, the desired Mannich products **35** was obtained with high enantiomeric ratios (> 98.5:1.5) and diastereomeric ratios of (> 95:5) in favor of the *syn*-product.



Scheme 1.13 Pyrrolidine-sulfonamide as an alternative catalyst to proline

S. Ley explored the same reaction to evaluate catalysts (**12**, **34**, and **36**) (**Figure 1.5**) 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 **33 (Scheme 1.13**) was obtained with diastereomeric ratios of (> 95:5) and with high enantiomeric ratios (> 97.5:2.5). It was heartening to see that even less catalyst loading of **35 (**1 mol %) was enough to catalyze the reaction efficiently and without loss of enantioselectivity. [89]

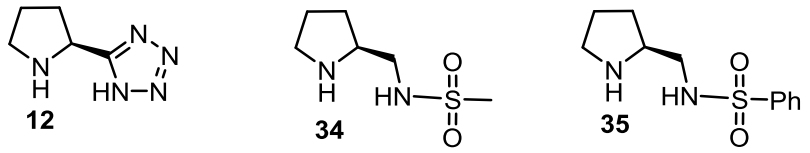
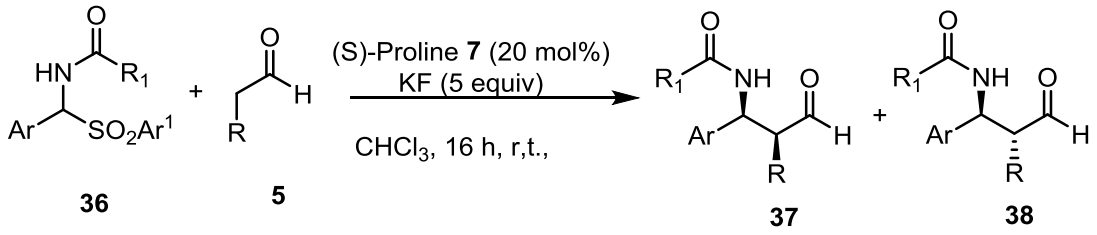


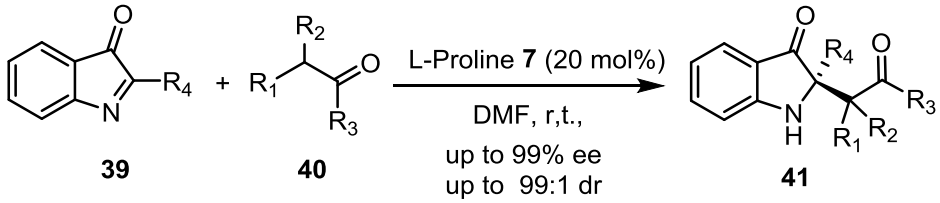
Figure 1.5 Improved catalysts for the Mannich reaction

In 2010, Zhao and coworkers reported the one-pot organocatalytic Mannich reactions between α-amidosulfones **36** and aldehydes **5** to furnish β-amino aldehydes **37** (major product) with good yields and high enantio- (99 % ee) and diastereoselectivity (95:5) (**Scheme 1.14**).[90]



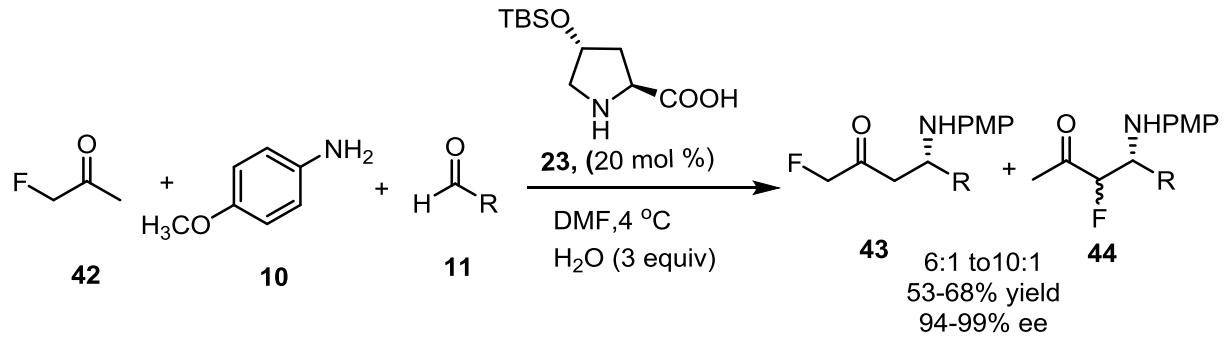
Scheme 1.14 Direct organocatalytic asymmetric Mannich reactions amido sulfones

In the same year, Li *et al*. developed proline catalyzed direct Mannich reaction of aldehydes or ketones **40** with 2-Aryl-3*H*-indol-3-ones **39** to afford the corresponding aza-quaternary carbon addition product **41** in good yields and excellent enantioselectivity (up to 99 %) (**Scheme 1.15**).[91]



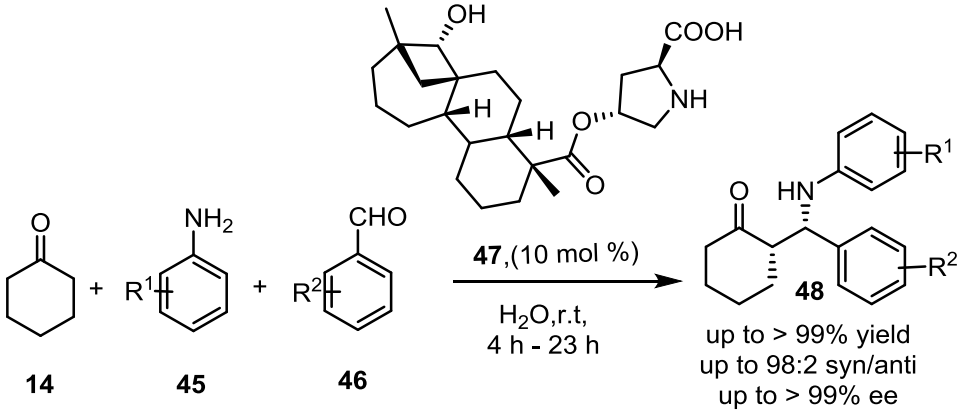
Scheme 1.15 Reaction of 2-Aryl-3*H*-indol-3-ones with ketones in the presence of Proline **7**

In 2011, Lu *et al.* found multi-component direct Mannich protocol with high enantioselectivity employing fluoroacetate **42**, *p*-anisidine **10**, and aldehydes **11** catalyzed by 4-siloxyproline **23** approach to have efficient access for pharmaceutically important fluorinated β-amino ketones **43, 44** (**Scheme 1.16**).[92]



Scheme 1.16 Synthesis of pharmaceutically important fluorinated β-amino ketones

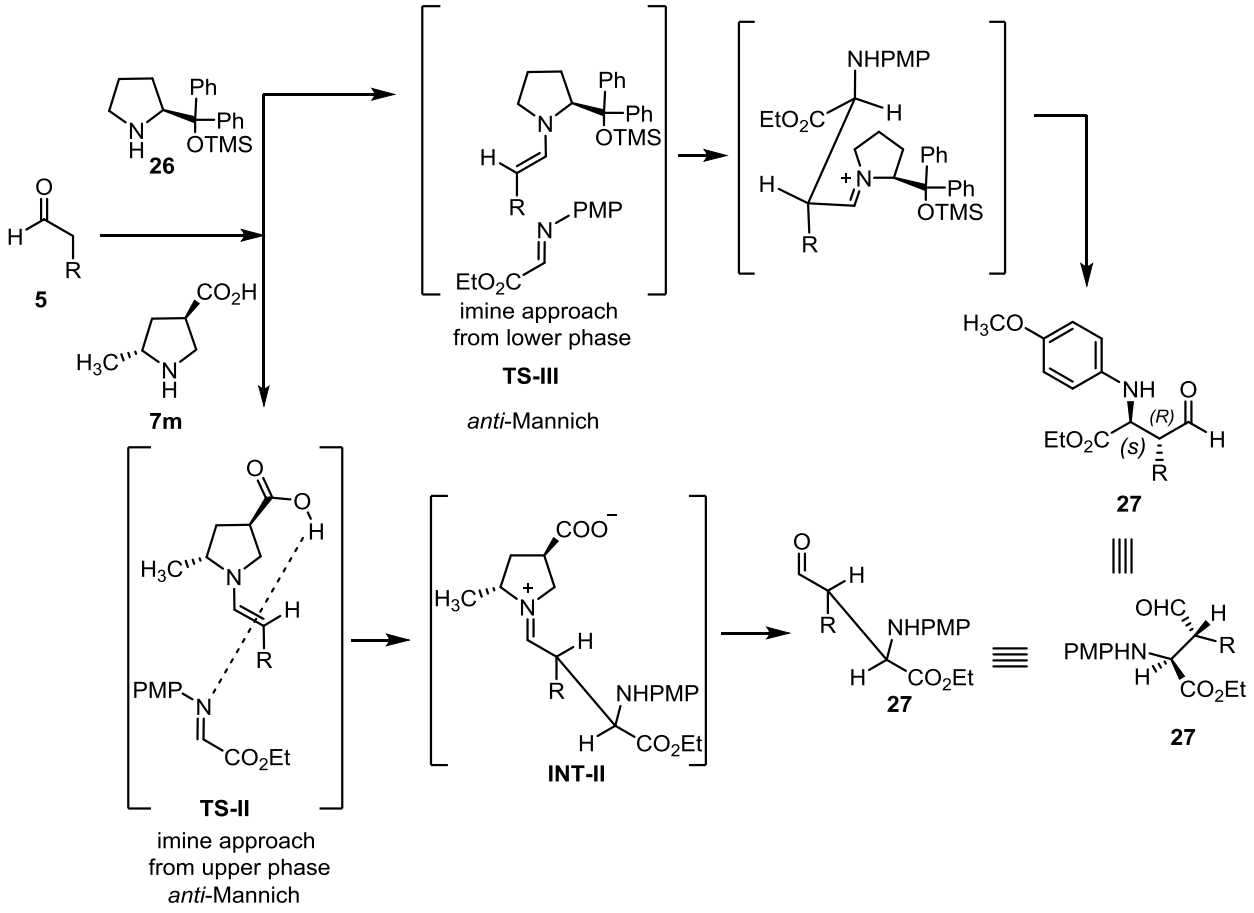
Recently, Y. J. An *et al.*[93] developed functionalized proline **47** catalyzed asymmetric three-component *syn*-Mannich reactions of cyclohexanone **14** and anilines **45** with aromatic aldehydes **46** in H_2O afforded product **48** with excellent diastereo- (*syn*/*anti* up to 98:2) and enantioselectivities (up to > 99 % ee) (**Scheme 1.17**).



Scheme 1.17 Synthesis of *syn*-Mannich products using amphiphilic organocatalysts

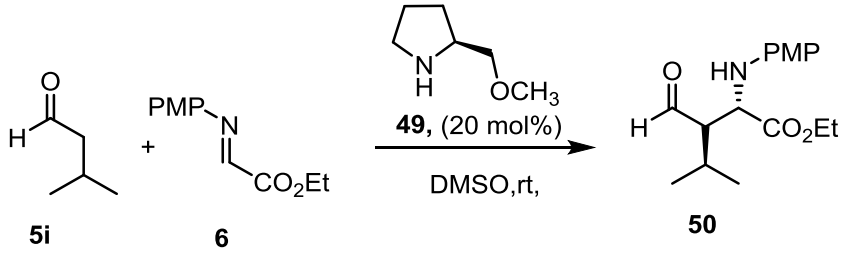
1.5.2 *Anti*-Mannich reaction

The *anti*-Mannich product **27** formed predominantly, if the reaction proceedes through either enamine transition state (TS-III), or sterically assisted transition state (TS-II) as shown in **Scheme 1.18.**



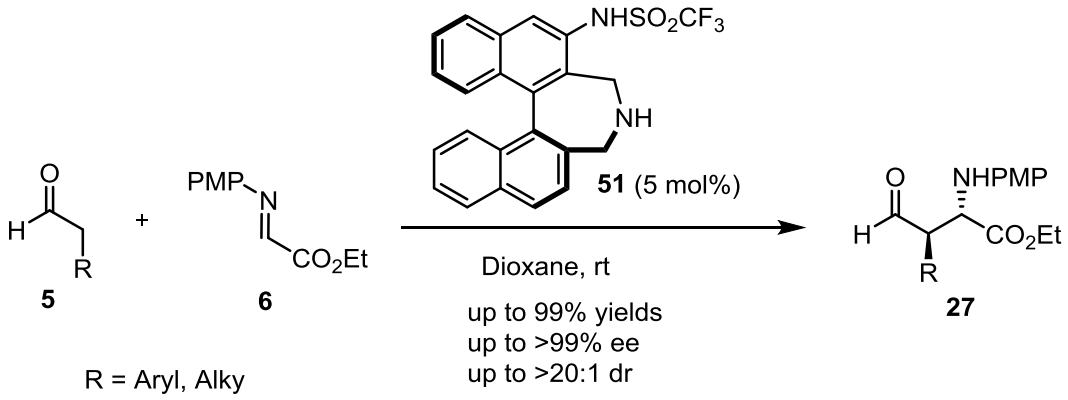
Scheme 1.18 Mechanistic aspect of organocatalytic asymmetric *anti*-Mannich reaction

The first *anti*-selective organocatalytic Mannich reaction was published by Barbas in 2002.[94] (*S*)-2-methoxymethylpyrrolidine **49** (20 mol %) served as a catalyst for Mannich reaction between aldehyde **5i** and imine **6** to give **50** (44-78 % yield, er up to 91:9) (**Scheme 1.19**). 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.



Scheme 1.19 First *anti* selective organocatalytic Mannich reaction

A highly *anti*-selective asymmetric Mannich reaction was developed by Maruoka and co-workers, using a novel axially chiral amino trifluoromethanesulfonamide **51** as amine catalyst.[95] This reactions between aldehydes **5** and *N*-PMP protected iminoglyoxylates **6** proceed smoothly to give α-amino aldehydes **27** with a high *anti*/*syn*-ratio and enantioselectivity. Maruoka's protocol with a plausible mechanistic insight provides an efficient way for the design and development of other *anti*-selective organocatalysts. Unlike proline and its derivatives, the catalyst **51** is based on a seven-membered ring. The chirality is derived from the BINOL-backbone.



Scheme 1.20 Asymmetric anti-Mannich reaction strategy for *anti*-Mannich base

Similarly, Barbas' and Jørgensen's developed C2 symmetric catalyst **52** for the direct *anti*-Mannich reaction with the same substrates (**Scheme 1.20 & Figure 1.6**).[97] The high enantiomeric ratios (up to > 99.5:0.5) was obtained with **52**, however catalyst **51** was found superior with regard to the activity and catalyst loading (0.2 to 5 mol %).

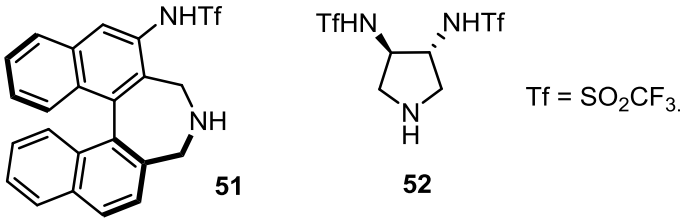
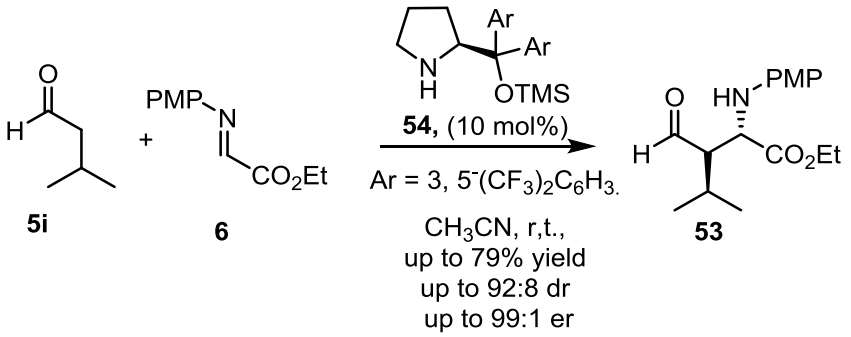


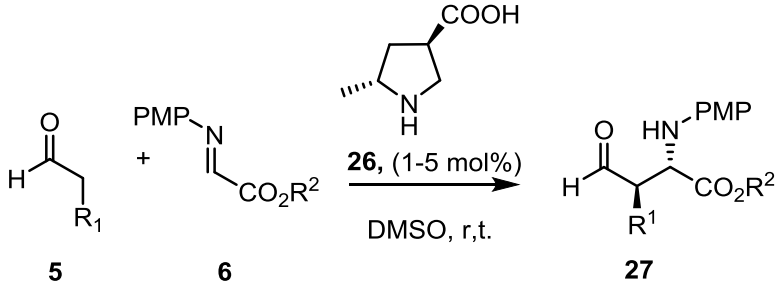
Figure 1.6 Axially chiral BINOL-derived catalyst developed by Maruoka group

Jørgensen's group later developed α,α-diarylprolinol silyl ether **54** as an efficient catalyst for high enantio- and diastereoselective *anti*-Mannich reaction between aldehyde **5i** and imine **6** to furnish **53** (**Scheme 1.21**).[96]



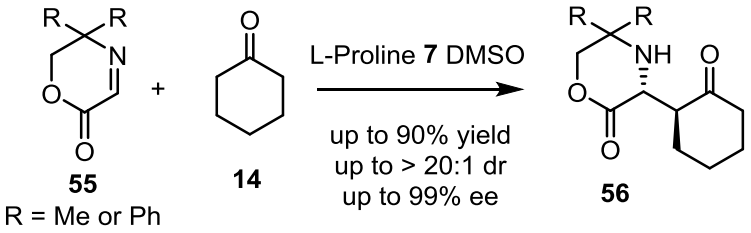
Scheme 1.21 α, α-Diarylprolinol silyl ether **54** for the *anti*-selective Mannich reaction.

The collaborative efforts from Barbas and Houk groups, resulted an efficient and highly selective catalyst **26.** This results a highly selective *anti*-Mannich reaction between aldehyde **5** and imine **6** through *syn*-enamine transition state (**TS-II, Scheme 1.18**) in presence of **26** to furnish product **27** excellent diastereo- (94:6 to 98:2) and enantioselectivities (> 98.5:1.5) (**Scheme 1.22**).[98]



Scheme 1.22 Proline derived amino acid **10** as highly active, *anti*-selective catalyst

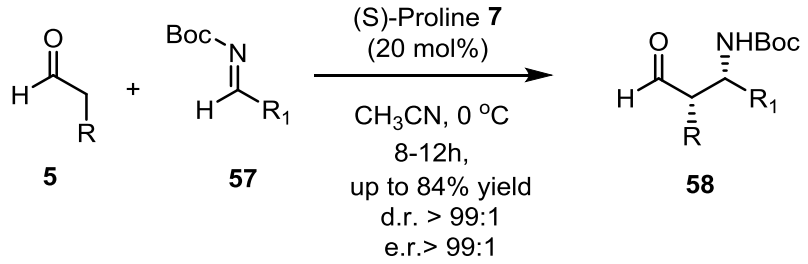
In the same year, Glorius *et al.* developed the utilization of cyclic imine acceptor **55** and unactivated ketones **14** for direct *anti*-Mannich reaction under proline-catalysis (**Scheme 1.23**).[99] These *anti*-Mannich products **56** corresponds to the protected α-*D*-amino acid. This protecting group for α-amino acids could be cleaved readily by hydrogenolysis in aqueous ethanol to furnish the free amino acid.



Scheme 1.23 Synthesis of chiral 3-substituted morpholin-2-ones

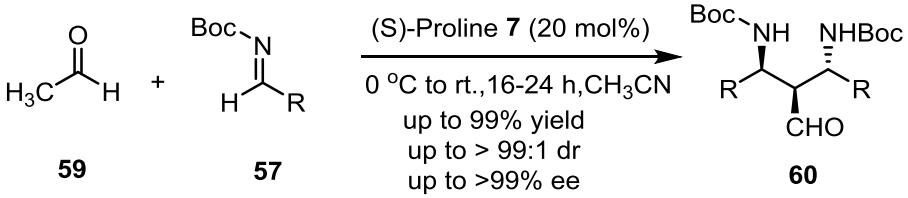
B. List and coworkers reported a highly diastereo- and enantioselective Mannich reaction of aldehydes **5** with *N*-Boc imines **57** using (*S*)-proline as catalyst gives crystalline β-amino

aldehydes **58** with high yields as shown in (**Scheme 1.24**).[100] The products of this reaction typically precipitate out from the reaction mixture as the reaction reached to completion. The products are useful intermediates in the synthesis of α-and β-substituted β-amino acids.



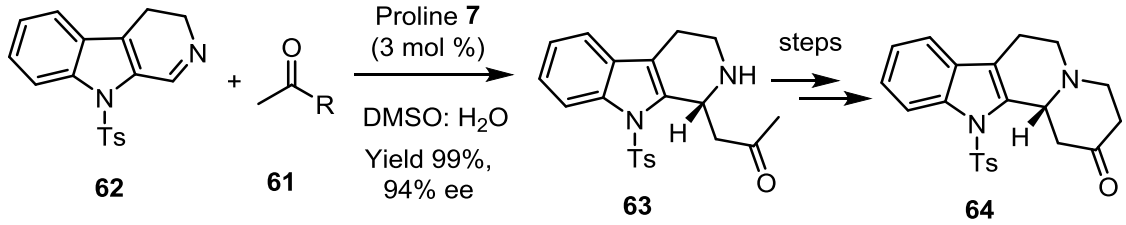
Scheme 1.24 Proline catalyzed asymmetric Mannich reaction of aldehyde and *N*-Boc-imines

List introduced the one-pot catalytic asymmetric synthesis of *pseudo*-C2 β,β'–symmetric diamino aldehydes **60** with extremely high stereoselectivities, starting from acetaldehyde **59** and either aromatic or aliphatic *N*-Boc imines **57**. The method was effectively extended to cross-Mannich reactions, furnishing β,β'-diamino aldehydes **60** containing three adjacent stereogenic centers (**Scheme 1.25**).[70]



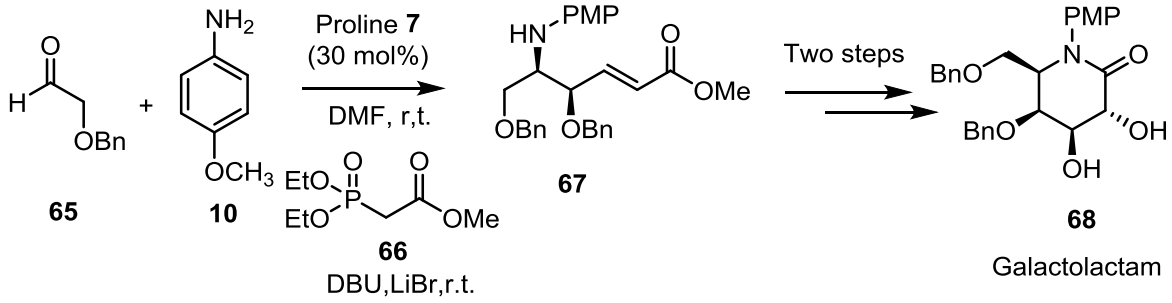
Scheme 1.25 Double Mannich reaction of acetaldehyde with N-Boc imine

Ohsawa and coworkers reported the (*S*)-proline **7** catalyzed direct Mannich reaction of 9-tosyl-3,4-dihydro-α-carboline **62** and acetone **61** to furnish indole based product **63** with high yields (99 %) and enantioselectivity (94 % ee) (**Scheme 1.26**).[101] In this process, a small amount of water was found to have adverse effect on the stereochemical outcome of the reaction. This protocol was further applied for the synthesis of medicinally important indole alkaloids **64**.



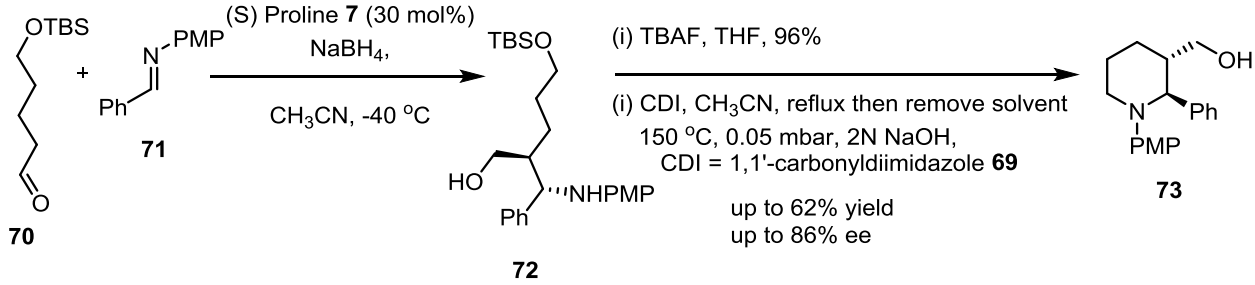
Scheme 1.26 Reaction of 9-Tosyl-3,4-dihydro-*â*-carboline with acetone

Córdova and co-workers developed a stereoselective catalytic one-pot tandem reaction that involves a Mannich, Horner-Wadsworth-Emmons (HWE), and subsequent Sharpless dihydroxylation sequence to provide optically active amino- and iminosugar derivatives **68**.[102] This method involves as (*S*)-proline **7** (30 mol %), α-benzyloxyacetaldehyde **65** reacted with *p*-anisidine **10** to give the corresponding Mannich product, which underwent Wittig reaction to furnish **67** with two stereogenic centers in good yield (64%), enantioselectivity (95% ee), and diastereoselectivity (4:1 dr). Subsequent Sharpless dihydroxylation and further acid-catalyzed cyclization provided the galactolactam **68** in good yield (74%) (**Scheme 1.27**).



Scheme 1.27 Synthesis of Galactolactam involving direct Mannich reaction

Recently, the amine catalytic approach has been further extended to synthesize the chiral piperidines **73** by Christmann and Xu groups.[103,104] The Christmann strategy involved as the *anti*-Mannich reaction of the linear aldehyde **70** with the imines **71** followed by $NaBH_4$ reduction and consequent intramolecular cyclization of amine moiety with alcohol in subsequent steps to furnish the functionalized chiral piperidines **73** as shown in **Scheme 1.28**

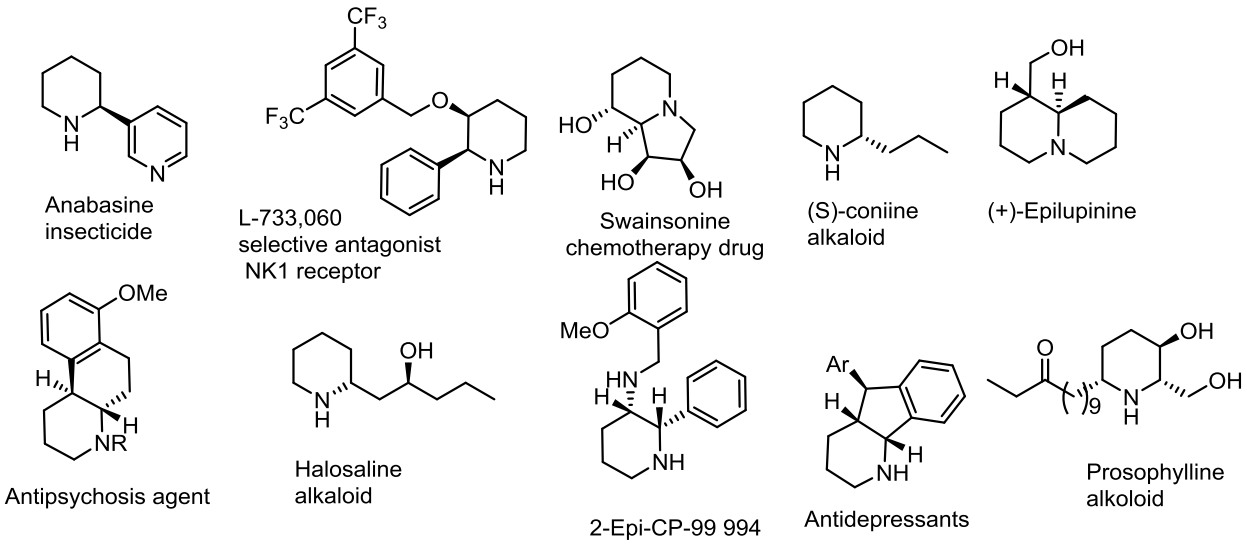


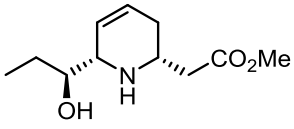
Scheme 1.28 Amine catalytic asymmetric synthesis of piperidines

1.6 Importance of nitrogen heterocycles

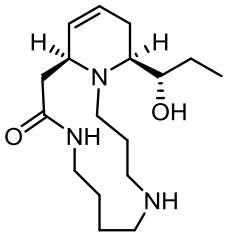
Diverse compounds like alkaloids, antibiotics, essential amino acids, vitamins, hemoglobin, hormones and many synthetic drugs and dyes contain heterocyclic rings as core skeletons.[105-107] The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs and a broad range of biologically important compounds.[108,109] 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.[110-113] Due to their useful biological applications, synthetic developments 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.[114-118] Among various sized nitrogen heterocycles, our work in this thesis is mainly focused on the construction of six-membered nitrogen heterocycles such as piperidines, 1,2-dihydropyridines (DHPs), 1,2,5,6-tetrahydropyridines (THPs), isoquinuclidines and their related medicinally important synthetic compounds. The importance of six-membered nitrogen heterocycles as natural and synthetic products is well documented in the literature. Some of the biologically important natural products containing six-membered *N*-heterocyclic ring as a main constituent in their structure are mentioned in the following **Figure 1.7**. [118-136]

Figure 1.7 Structures of some six-membered bioactive nitrogen heterocycles

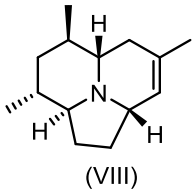




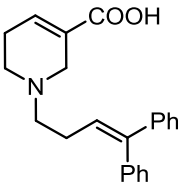
(-)-Methyl palustramate
Alkaloid



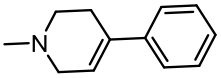
(+)-Palustrine
Alkaloid



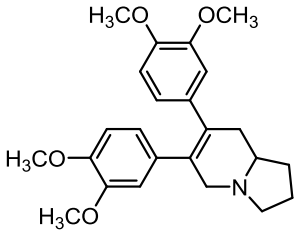
(VIII)
(+)-Alkaloid 205B



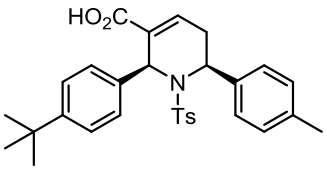
(IX)
SKF 100330-A



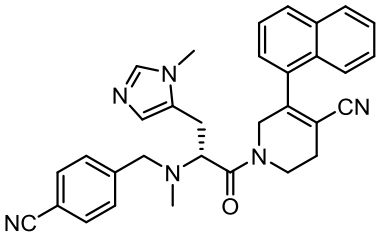
MPTP
Experimental model of
neurodegeneration



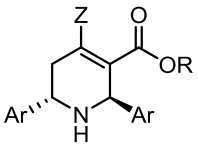
Septicine
Alkaloid



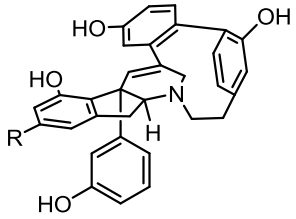
Anticancer agent



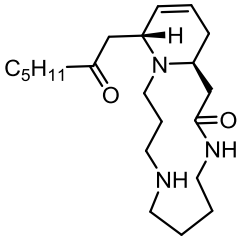
Farnesyl tranferase
inhibitor



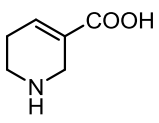
(IV) Z = NHAr
(V) Z = OH
antimalarial and
anticancer activity



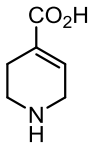
(I) R = H, Haouamine A
(II) R = OH, Haouamine B



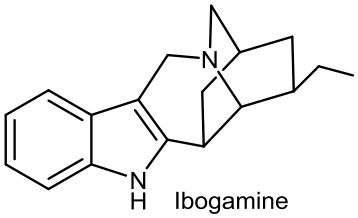
(III)
Anhydrocannabisarivene



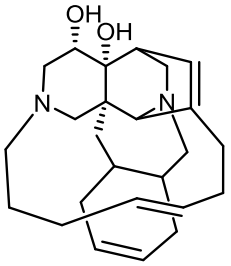
(VI)
Guvacine



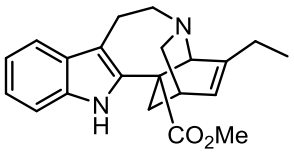
(VII)
Isoguvacine



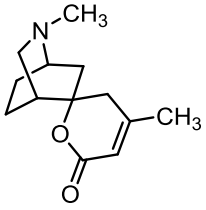
Ibogamine
Alkaloid



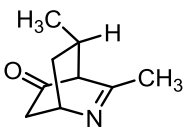
xestocyclamine A
Alkaloid



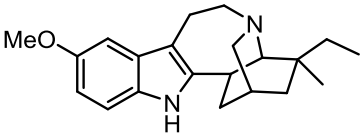
catharanthine
Alkaloid



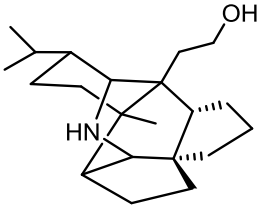
Dioscorine
alkaloid



Mearsine
alkaloid



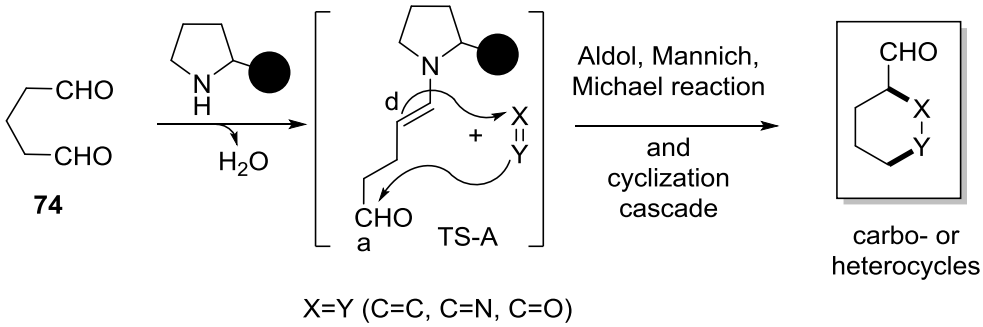
Ibogaine
Alkaloid



caldaphnidine D

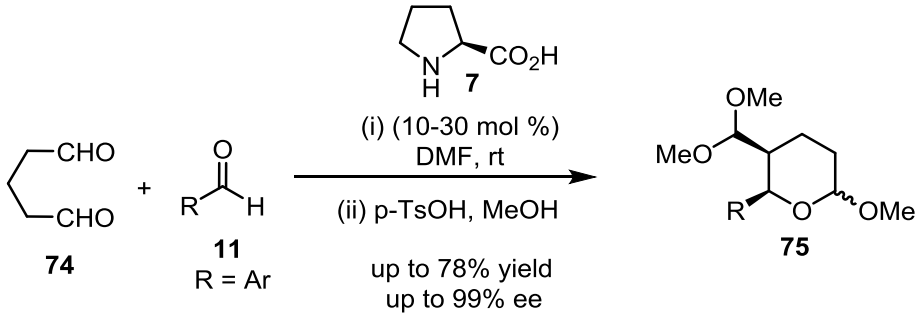
1.7 Glutaraldehyde in amine catalytic intermolecular transformations

Linear dialdehydes and their derivatives have been recognized as important substrates in the area of synthetic organic chemistry.[137] 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 suitable cross linking agent for the enzymes immobilization because it possesses unique chemical behavior in aqueous solution.[138,139] Additionally, glutaraldehyde has also been utilized successfully for the quick synthesis of small heterocyclic scaffolds as well as useful alkaloids.[140-144] Since, the entire thesis work was done by using glutaraldehyde as one of the substrates, more attention is devoted to explore 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 1.29)** from one of the aldehyde group whereas another aldehydic moiety acts as acceptor with various dipolarophile (X=Y), furnished carbocyclic/heterocyclic ring systems in one-pot operation without much protection-deprotection steps. The application of glutaraldehyde **74** in amine catalyzed domino transformation is quite obvious as it can give a rapid access to medium sized carbo-and heterocyclic ring systems depend on counterpart dipolarophile X=Y (C=C, C=N, C=O) used in the reaction which was collectively reviewed by our group recently.[155]



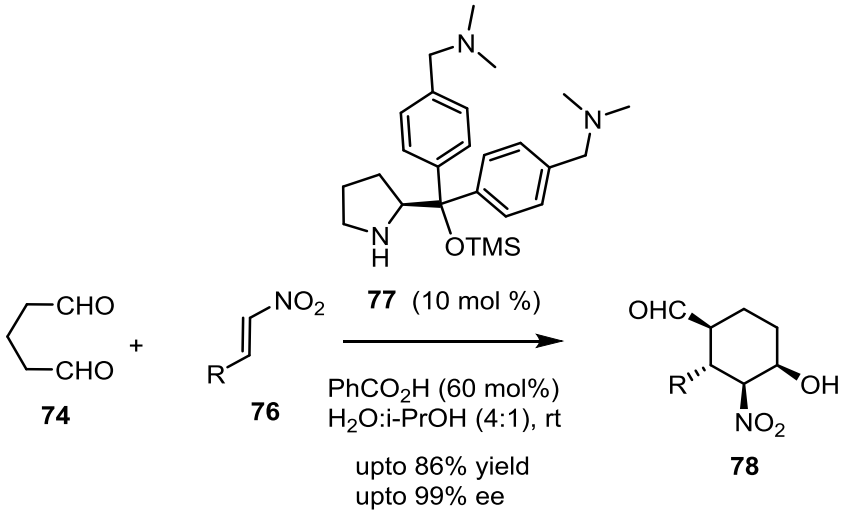
Scheme 1.29 Amine catalyzed intermolecular transformations through glutaraldehyde

Hayashi and co-workers developed amine catalyzed asymmetric synthesis of tetrahydropyrans **75** through domino transformations, in which glutaraldehyde **74** was considered as one of the important synthetic counterparts (**Scheme 1.30**).[145] This process involved proline **7** mediated direct aldol reaction of **74** with aromatic aldehydes **11**, followed by acid catalyzed acetalization reaction provided *cis*-tetrahydropyrans **75** with high selectiviteis.



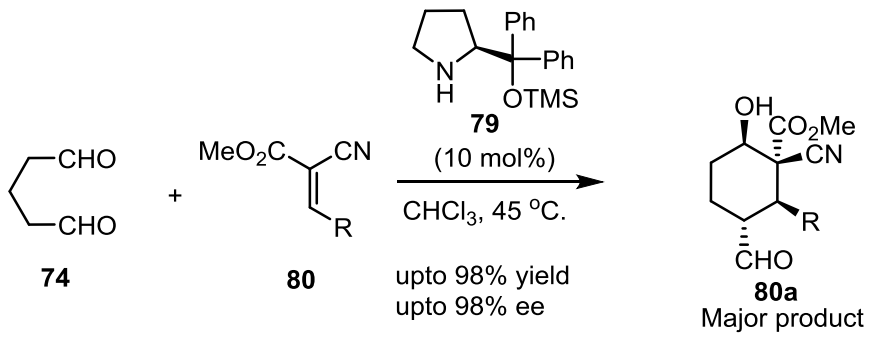
Scheme 1.30 Amine catalyzed synthesis of tetrahydropyran from glutaraldehyde

A water soluble organocatalytic approach for functionalized cyclohexanes **78** from glutaraldehyde **74** and activated alkene **76** was developed by Ni and co-workers using the water soluble and recyclable organocatalysts **77**. (**Scheme 1.31**).[146] While, the catalyst **77** loading (10 mol%) is more costly synthesis of catadownside of the approach. Use of water as a safe and nontoxic solvent along with catalyst recycling from four to seven times without much variation in yields and selectivity make this protocol more practical.



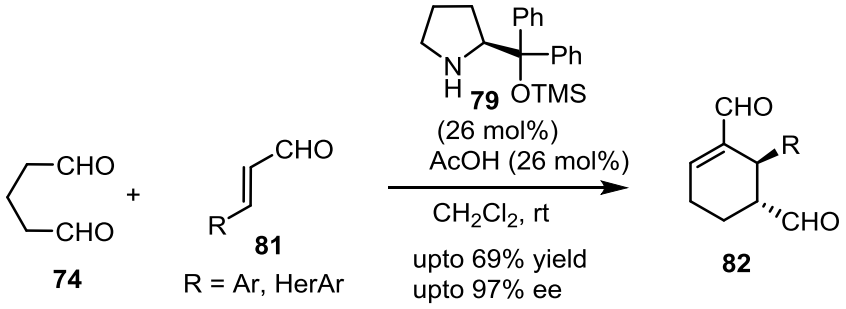
Scheme 1.31 Intermolecular transformation of glutaraldehyde for functionalized cyclohexanes

Cordóva and co-workers explored the highly enantioselective approach to access functionalized cyclohexanes **80** from glutaraldehyde **74** under amine catalyzed domino Michael/aldol procedure (**Scheme 1.32**).[147] These functionalized chiral products **80a** well decorated with cyano, formyl, hydroxyl, and ester groups, were generated with high yields and enantioselectivities with various alkylidenemalonates as suitable dipolarophiles. The resulting products contained four contiguous chiral centres including one quaternary centre, could be useful intermediates in synthesis.



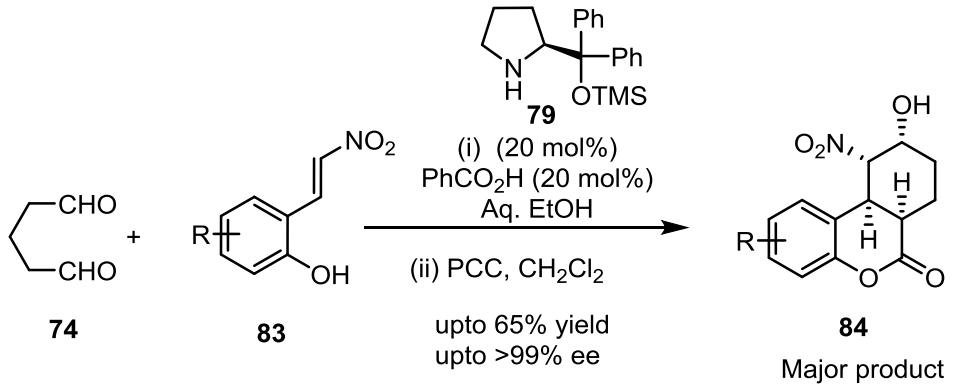
Scheme 1.32 Amine catalyzed intermolecular transformation of glutaraldehyde

Hong and co-workers have made significant contribution in the development of amine catalyzed asymmetric cascade transformations, where linear dialdehydes attained enormous importance in the construction of complex molecules. The initial application of glutaraldehyde in the quick synthesis of functionalized cyclohexene derivatives as domino strategy was developed (**Scheme 1.33**).[148] The reaction involved amine catalyzed Michael reaction of glutaraldehyde **74** with 3-arylpropenal **81** followed by intramolecular aldol condensation to access **82** in high yields and excellent enantioselectivity.



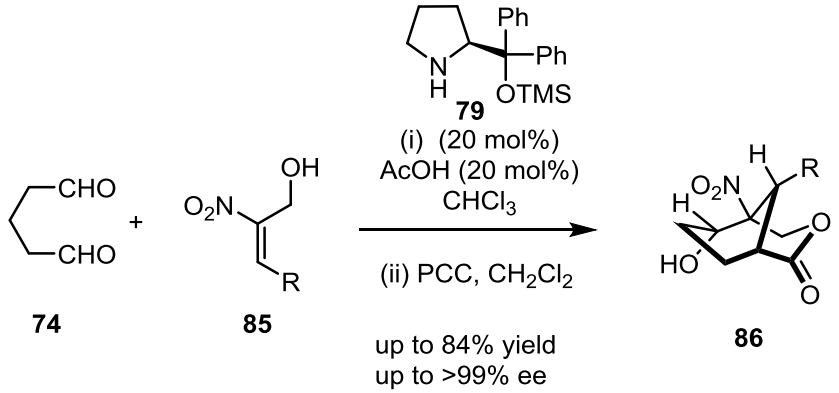
Scheme 1.33 Amine catalyzed intermolecular transformation of glutaraldehyde for chiral cyclohexenes

An amine catalyzed domino Michael-acetalization-Henry reaction between easily available glutaraldehyde **74** and *ortho*-hydroxynitrostyrenes **83** to synthesize complex tetrahydro-6*H*-benzo[*c*]chromen-6-ones **84** in asymmetric fashion was reported recently by B. C. Hong group. (**Scheme 1.34**).[149] Interestingly, this cascade process performed exceptionally well generated four contiguous chiral centers through three bonds forming steps with excellent stereoselectivity.



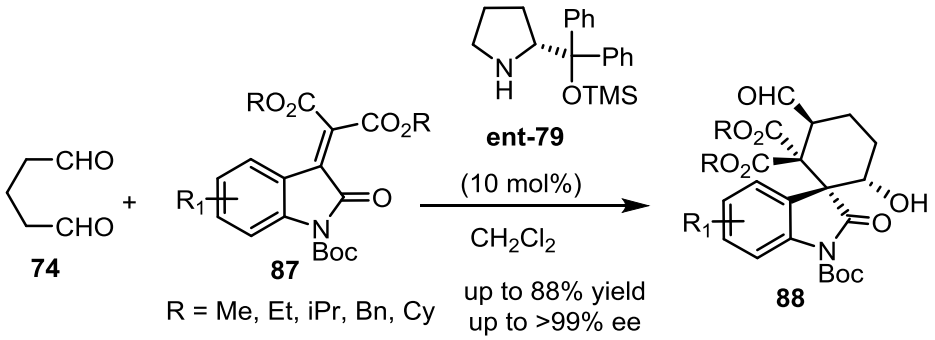
Scheme 1.34 Amine catalyzed domino reaction of glutaraldehyde

Very recently, Hong *et al.* developed, another interesting application of glutaraldehyde **74** in amine catalyzed transformation to 3-oxabicyclo[3.3.1] nonan-2-ones **86** consisting four consecutive stereogenic centres (**Scheme 1.35**).[150] This method involved organocatalytic cascade Michael-Henry acetalization-oxidation reaction of 3-aryl-2-nitroprop-2-enols **85**, furnished bridged bicyclic systems **86** 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 wide range of synthetic applications.



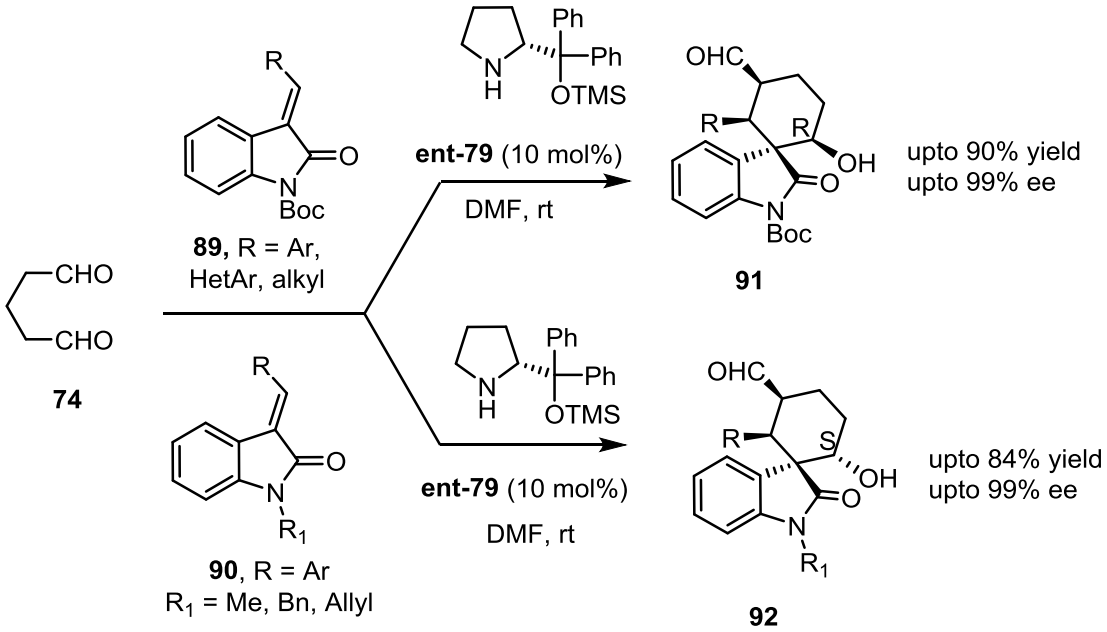
Scheme 1.35 Intermolecular transformation of glutaraldehyde for oxa-bicyclic compounds

Wang and co-workers exploited the ability of glutaraldehyde **74** in organocatalytic domino Michael/Aldol cyclization using isatin-derived alkenes **87** as Michael acceptors (**Scheme 1.36**).[151] A series of functionalized spirocyclohexane oxindoles **88** decorated with formyl, hydroxy, and ester groups were synthesized in asymmetric fashion using amine catalyst **ent-79** (10 mol%) catalysis with high yields and excellent selectivity.



Scheme 1.36 Amine catalyzed intermolecular transformation of glutaraldehyde for the spiro compounds

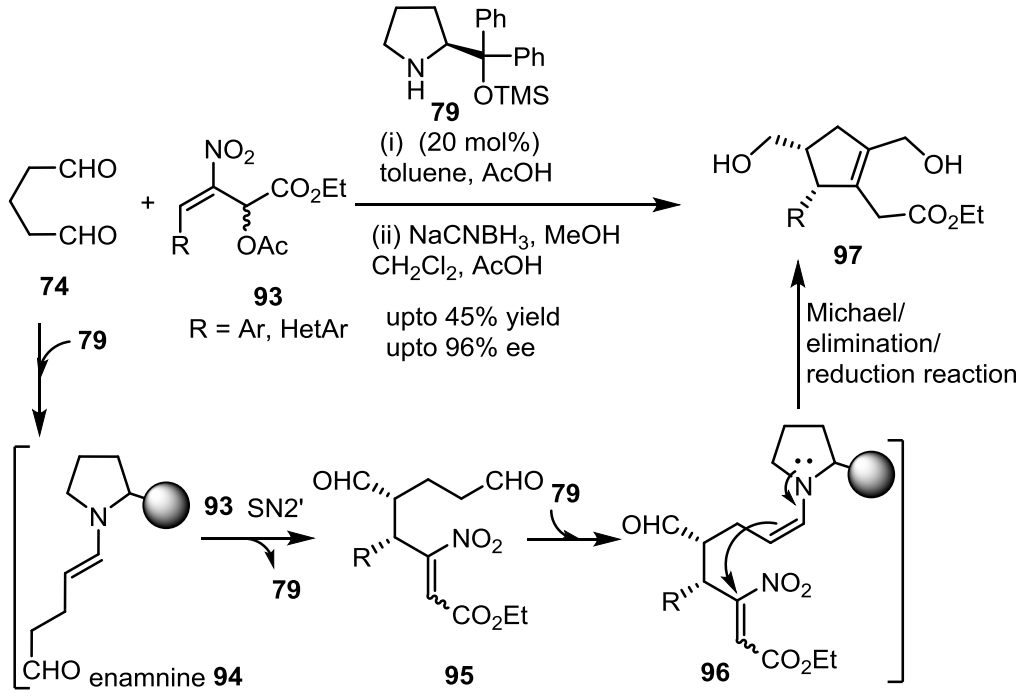
In a very similar protocol, Ghosh *et al*. described the enantioselective synthesis of spirocyclohexane oxindoles **91, 92** comprise of multiple stereocenters including a spiro-quaternary centre from the glutaraldehyde **74** in high yields and excellent enantioselectivities.[152] Interestingly, *N*-protecting groups on the oxindoles moiety played a critical role on aldol ring closure leading to ultimate stereochemical outcome of the hydroxyl centre.



Scheme 1.37 glutaraldehyde as a key substrate for spiro compounds

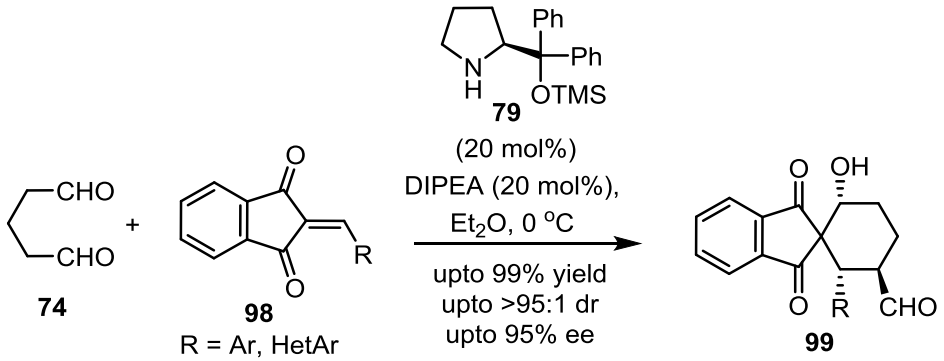
Chen and co-workers developed an amine **79** catalyzed cascade transformation for the synthesis of functionalized cyclopentanes from glutaraldehyde **74** and racemic nitroallylic acetates **93** (**Scheme 1.38**).[153] In this process kinetic resolution of racemic **93** was accomplished through the S_N2' reaction followed by intramolecular Michael addition-elimination process in presence

of diphenylprolinol silyl ether **79** gave tetrasubstituted-cyclopentenes **97** with satisfactory yields and high enantioselectivity. The less reactive enantiomeric substrate was generally recovered with good to excellent optical purities. In mechanism, enamine **94** generated from **74** and **79** gave S_N2' reaction with **93**, while another aldehydic moiety underwent intramolecular Michael addition-elimination through intermediate **95** and **96** to give **97** after in situ reduced with $NaBH_4$.



Scheme 1.38 Amine catalyzed synthesis of functionalized cyclohexenes from glutaraldehyde

Very recently, another interesting application of glutaraldehyde **74** for the synthesis of spirocyclohexane-carbaldehydes **99** using amine **79** catalysis was developed by Chen group (**Scheme 1.39**).[154] The amine **79** catalyzed Michael/Aldol domino sequence between glutaraldehyde **74** and 2-arylideneindane-1,3-diones **98** as [4+2] annulations provided spirocyclohexane-carbaldehydes **99** with high yield and selectivity's (up to 95% ee). The overall selectivity of the reaction was found to be additive and temperature dependent, while **98** derived from aryl/heteroaryl groups were employed successfully.



Scheme 1.39 Spirocyclic scaffolds from amine catalyzed transformation of glutaraldehyde

1.8 Conclusion and conception

The focus of this Ph.D. work is to expand the scope of amine catalysis towards the synthesis of six-membered nitrogen heterocycles and related small molecule natural products (SMNPs). The overall strategy for six-membered *N*-heterocyclic ring system proceeds through proline catalyzed direct Mannich-cyclization reaction between glutaraldehyde and imine, followed by site selective reduction and oxidation sequence. Further, the developed methodology was utilized for the synthesis of some biologically active natural and synthetic products from inexpensive and commercially available starting materials such as glutaraldehyde, which acts as 1,4-carbon *donor-acceptor* precursor and various imines. The present protocol has following advantage through organocatalysis, such as the readily availability, cheap, bench-stable catalysts, and mild reaction conditions which are insensitive to air and moisture. It is important to note that organocatalysis was used to solve long-standing challenges, in which metal-mediated and other approaches proved to be only moderately effective or failed altogether. Thus, a tremendous recent development shows an increased interest in the field of organocatalytic cascade reactions. In particular, the development of organocatalytic direct Mannich reaction and its involvement in one pot domino reactions could be an effective way to synthesize *N*-heterocyclic compounds in asymmetric as well as in non-asymmetric fashion. This overview summarized the diverse procedures reported for direct Mannich reactions using the concept of organocatalysis over last more than one decade. Owing to the increased interest in nitrogen heterocycles, as these skeletons 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. 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.

Recently, our group have extensively utilized glutaraldehyde for direct Mannich reaction followed by oxidation, or reduction, or domino-reaction sequence for the synthesis of *N*-heterocyclic ring systems (**Figure 1.8)** which will be discussed chapter wise in this thesis.

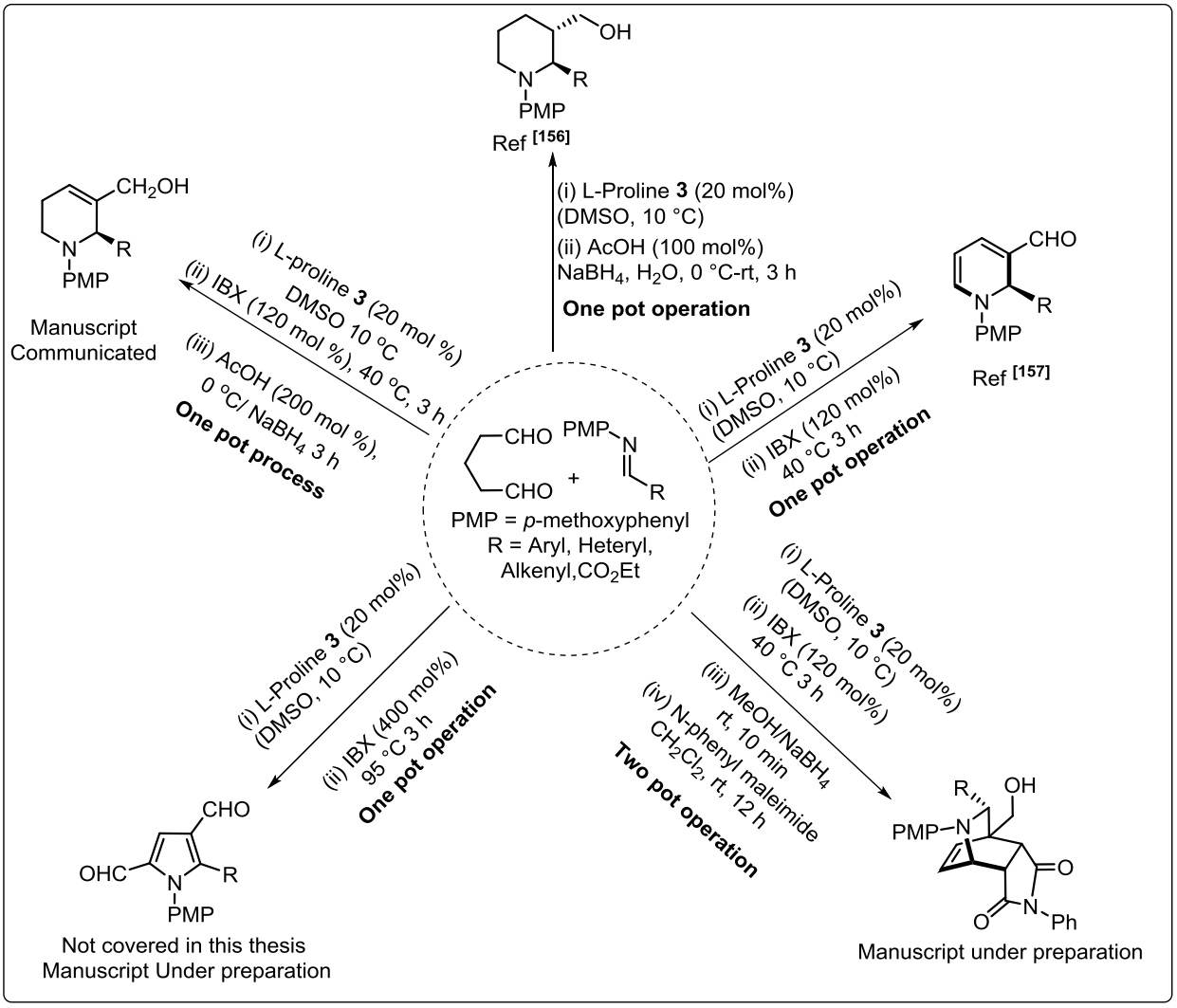


Figure 1.8 Overall representation of thesis work through proline catalyzed transformations

In the following chapters, an overview of heterocyclic compounds and their importance, the literature proceedings related to the heterocyclic ring system, followed by the description and discussion of our own work will be presented.

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Chapter - 2

Proline Catalyzed Asymmetric Synthesis of 2,3-disubstituted Piperidines and Related Alkaloids

2.1 Introduction:

N-Heterocyclic compounds have attracted considerable attention owing to their utilization in pharmaceutical chemistry, material chemistry, and synthetic organic chemistry. Especially six membered nitrogen heterocycles like piperidines are important compounds found in several biologically active compounds. Piperidine, a six membered saturated *N*-heterocycle molecule with the molecular formula $(CH_2)_5NH$, is a color less liquid with a pepper-like odor. Piperidines are widely used building blocks in the synthesis of organic compounds, including pharmaceutical drugs.[1,2] Functionalized saturated piperidines are common scaffolds of several natural products and widely distributed in a number of biologically active natural and synthetic compounds.[3-5] Few biologically important piperidines are shown in **figure 2.1.**

A large number of therapeutic alkaloids are also based on a piperidine core, such as the opium poppy alkaloid *morphine* and Cinchona alkaloid *quinine*. A brief inspection of piperidine-based natural products illustrates that these compounds exhibit a very broad range of molecular complexities and architectures and, therefore, such compounds represent significant synthetic challenges. Because of these reasons, the search for general, efficient and stereoselective approaches of substituted piperidine synthesis has attracted the attention of the synthetic community for many years. A large number of strategies are available for the construction of six-membered *N*-heterocyclic ring systems.

Due to increasing environmental concerns, the development of easy, economical and environmentally benign synthetic methods have become very important in organic chemical research. Interestingly, cycloaddition reactions are the most versatile methods for the synthesis of cyclic ring systems because of atom economy. In particular, piperidine can be prepared by [3+3],[6,7] [4+2][8-10] and [5+1][11] cycloadditions, along with other methods. Among these cycloaddition reactions, Diels-Alder [4+2] cycloaddition reaction is the most versatile method to prepare this six membered *N*-heterocycles and extensively studied.[12-16] Hence, our attention was to choose this cycloaddition method for the piperidine synthesis.

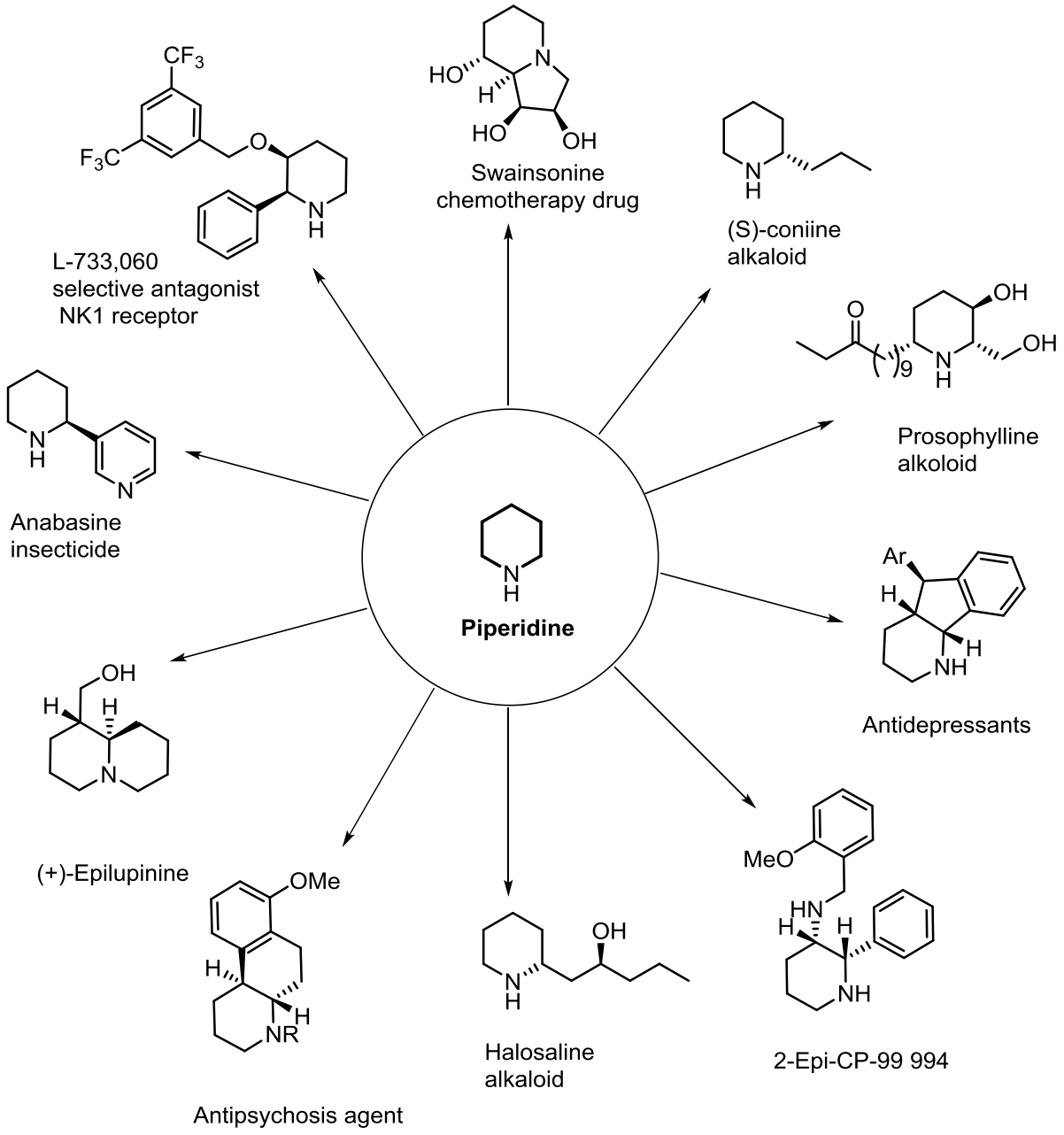


Figure 2.1 Representative examples of bioactive substituted piperidines

2.2 Diels-Alder [4+2] cycloaddition reactions

Diels-Alder [4+2] cycloaddition reactions are the most popular methods for the synthesis of cyclic ring systems, in particular, for the synthesis of substituted piperidine ring. Here, we have categorized the possible [4+2] cycloaddition reactions for piperidine ring based on the literature available as shown in **figure 2.2.**

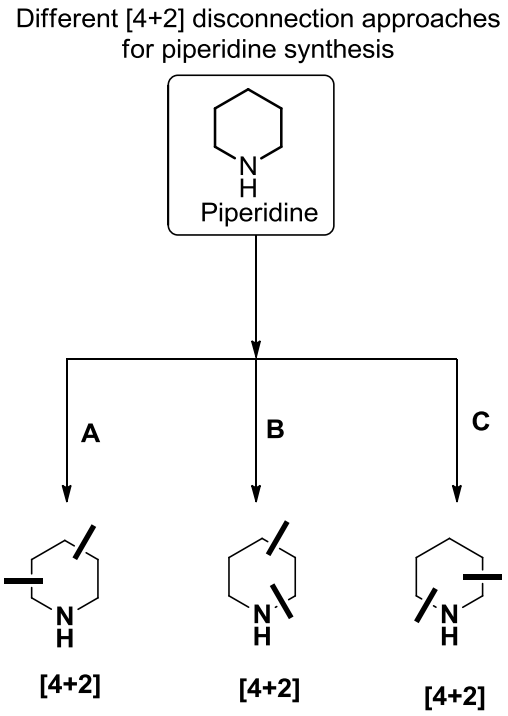
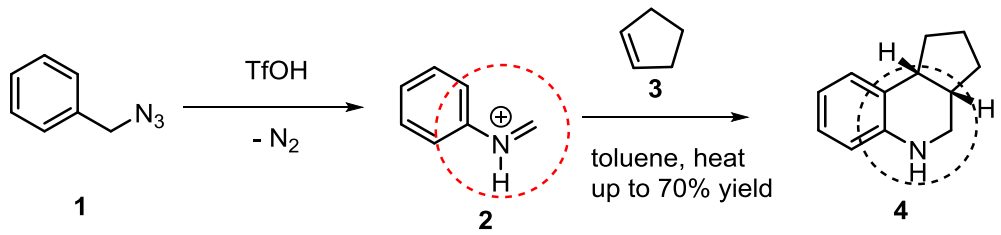


Figure 2.2 Different [4+2] cycloaddition approaches for the piperidine ring system

There are few formal [4+2] cycloaddition reactions are also reported for piperidine ring system.

2.2.1 [4+2] disconnection approach A: [Imino-Diels-Alder reaction]

There are synthetic methods available for the synthesis of piperidines through disconnection strategy **"A"** as shown in **figure 2.2.** [17-20] One of the recent examples in this direction is the use of N-phenyl methanimines **2** acts as 1,4-carbon dipole with an alkene **3** for Aza-Diels–Alder [4+2] cycloaddition reaction to yield substituted piperidine system **4** in good yields.[17]

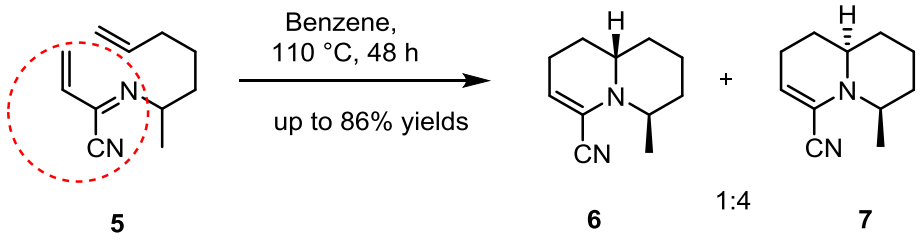


Scheme 2.1 [4+2] cycloaddition of N-phenyl methanimines with alkenes

2.2.2 [4+2] disconnection approach B: [Aza-Diels-Alder reaction]

There are synthetic methods found for the synthesis of piperidines through disconnection strategy **"B"** as shown in **figure 2.2.**[21,22] The *N*-alkyl prop-2-en-1-imines **5** undergoes thermally

allowed [4+2] Aza–Diels–Alder cycloaddition for the construction of functionalized piperidines **6, 7.** [21]



Scheme 2.2 Intra molecular [4+2] cycloaddition of N-alkyl prop – 2-en-1-imines

2.2.3 [4+2] disconnection approach C: [4+2] cycloaddition/formal [4+2] cycloaddition

There are synthetic methods found for the synthesis of piperidines through disconnection strategy **"C"** as shown in **figure 2.2.** The involvement of imine in [4+2] cycloaddition/annulation for the synthesis of piperidine system has not been explored extensively. Few reports are available for the synthesis of piperidine *via* [4+2] cycloaddition/annulation involving imine which we categorized here. Four types of methods are found in the literature for the synthesis of piperidine ring system which involving imine as one of the substrates which are described in **Figure 2.3**.

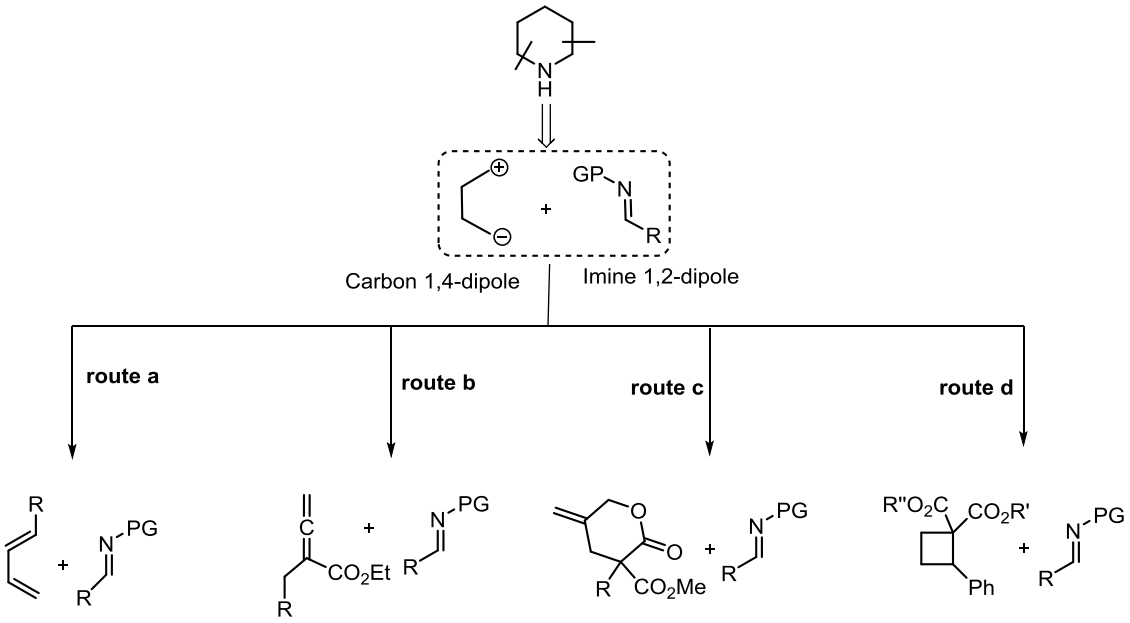


Figure 2.3 Existing approaches to synthesize piperidine via Path C

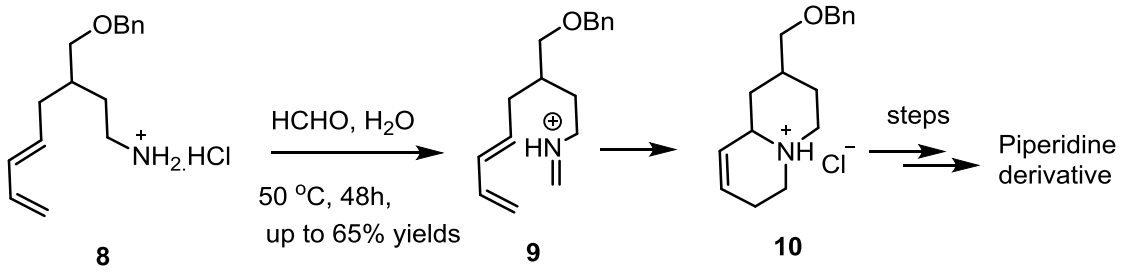
a. Imino Diels-Alder [4+2] cycloaddition reactions.

b. Phosphine catalyzed formal [4+2] cycloaddition reactions.

c. Metal catalyzed formal [4+2] cycloaddition reactions.

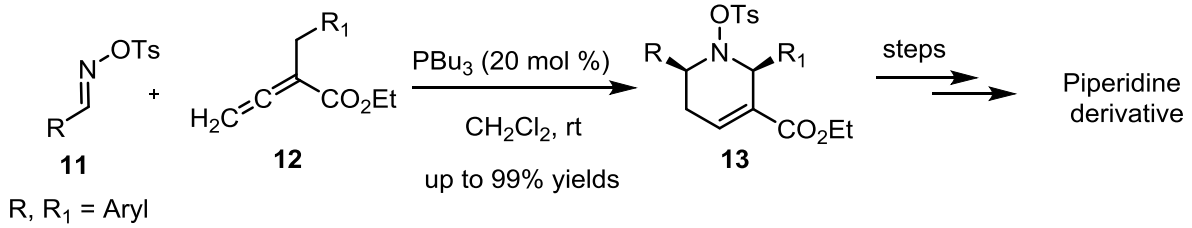
d. Lewis acid catalyzed formal [4+2] cycloaddition reactions.

(**a**). Imino-Diels-alder reaction was established by the different research groups and explored comprehensively.[23] Imine **9** as dienophile **(route-a)(Figure 2.3),** with intra molecular carbon diene, is probably a Hetero Diels-Alder cycloaddition is useful in the synthesis of several natural products containing piperidine ring system as shown in **Scheme 2.3**.



Scheme 2.3 Imino Diels-Alder approach for the synthesis of piperidine

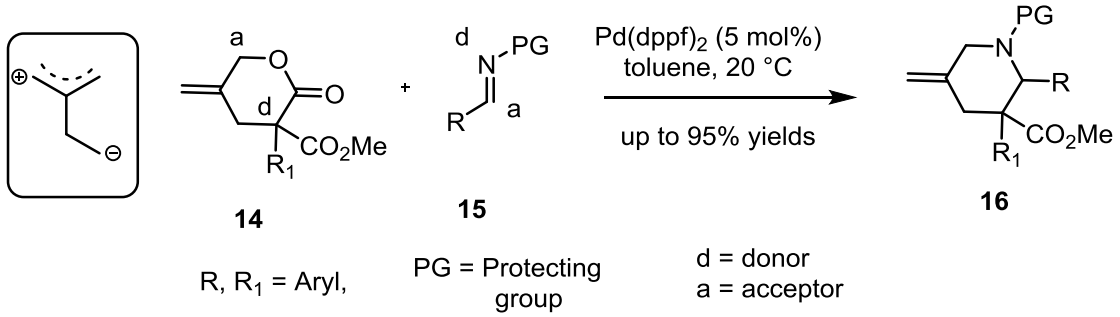
(**b**). Recently, Kwon group reported a [4+2] cycloaddition strategy for piperidines synthesis. The process involved a phosphine-catalyzed *in situ* generated 1,4-carbon dipole and subsequent reaction with imines **11**, produced functionalized piperidines **13**[24] in excellent yields (**route-b**) (**Figure 2.3**). This method also needs several steps to access piperidine as shown in **Scheme 2.4**.



Scheme 2.4 Phosphine-catalyzed [4+2] cycloaddition/annulation approach for the piperidine ring system

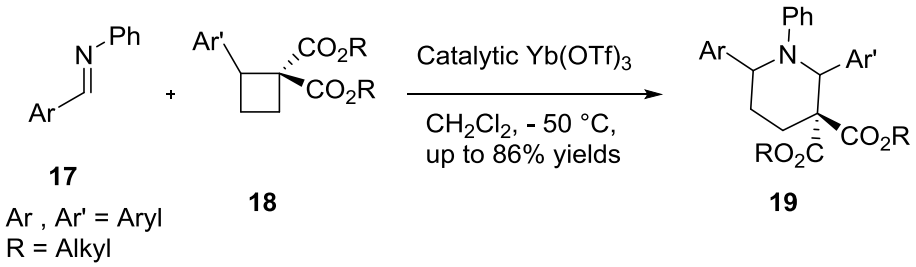
Particularly, [4+2] cycloaddition/annulation reactions such as: *i*) Imino-Diels-Alder reaction,[25-28] and *ii*) Phosphine-catalyzed *in situ* generated 1,4-carbon dipole and subsequent reaction with imines,[29-32] are the two methods accesses tetrahydropyridines which required further steps to convert into their resultant piperidines.

(**c**). The developed method involved through an *in situ* generation of 1, 4-carbon dipole *via* the metal-catalyzed decarboxylative ring-opening of γ-methylidene-δ-valerolactones and subsequent [4+2] annulation with imines **15** to synthesize 2,3-substituted piperidines in *non-asymmetric* fashion from Prof. T. Hayashi group in 2009.[32] The substrate **14** was used as a suitable 1,4-dipoles in this strategy as shown in **Scheme 2.5**. (**route-c**), (**Figure 2.3**).



Scheme 2.5 Metal-catalyzed approach for the synthesis of piperidine

(**d**). The synthesis of substituted piperidines **19** was achieved using triflates as a Lewis acid catalyst via strained ring opening of butyl esters **18** followed by Mannich reaction with imines **17** followed by cyclization which was reported by Pagenkopf group (**route-d**) (**Figure 2.2**).[33] This method accesses the saturated six-membered N-heterocycles.

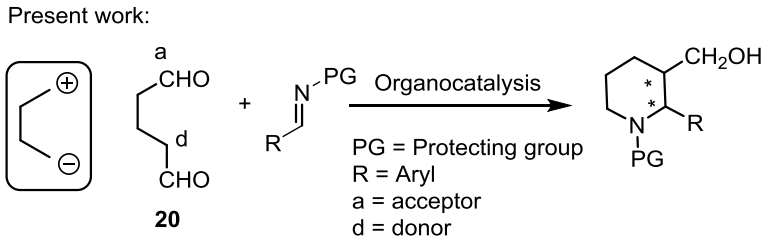


Scheme 2.6 Lewis acid catalyzed approach for the synthesis of piperidine ring system

Despite high utility, more strictly, methods a, and b in **figure 2.3** gave only direct access to tetrahydropyridines instead of piperidines. On the other hand, complementary [4+2] annulation of suitable all-carbon 1,4-dipoles with imines to synthesize piperidines directly, have not been studied extensively due to the unavailability of suitable 1,4-dipoles. Hence, our attention was to explore the synthetic routes for piperidines by using imine as one of the synthetic substrates as dienophile (2 atomic species, 1,2-dipole having nitrogen source) with other 1,4-carbon dipole. Hence, the development of a catalytic asymmetric method for 2,3-substituted piperidines through 1,4-carbon *donor-acceptor* annulation with imines, from simple and easily available materials is

still in very high demand. Additionally, 2,3-substituted piperidine skeleton present in a number of compounds having biological significance (**Figure 2.1**). However, few lengthy and limited methods are available to synthesize this ring system.[34-38]

Last few years are perceived for the remarkable growth of organocatalytic cascade or tandem transformations, which are now considered to be the most effective ways to design new catalytic asymmetric synthetic pathways.[39-42] Recently, few attractive organocatalytic cascade approaches have been reported by different groups to synthesize optically enriched piperidines.[43-50] Herein, we thought to develop a proficient one-pot organocatalytic Mannich-reductive cyclization sequence for the asymmetric synthesis of 2,3-disubstituted piperidines from imines and aqueous glutaraldehyde **20** (**Scheme 2.7**). Glutaraldehyde has been used earlier for *N*-substituted piperidine synthesis [11] and recently been employed in several other organocatalytic transformations.[51-57]



Scheme 2.7 1,4-carbon *donor-acceptor* approach with imines as formal [4+2] cycloaddition for piperidines

2.3 Results and discussions:

In our efforts towards *N*-heterocyclic compounds synthesis,[58-64] we thought to extend our idea to use glutaraldehyde as a suitable bi-functionalized compound for the organocatalytic one-pot transformations. Here, we expected that, the glutaraldehyde **20** is a synthetically useful 1,5-dicarbonyl compound, could be explored as *in situ* 1,4-carbon *donor-acceptor* precursor with imines to synthesize piperidines. This reaction involves proline-catalyzed direct Mannich reaction and acid catalyzed intramolecular reductive cyclization as one pot formal [4+2] cycloaddition. The screening of catalysts, solvents, and temperature with *N*-PMP aldimine as model substrate were investigated and summarized in **Table 2.1**.

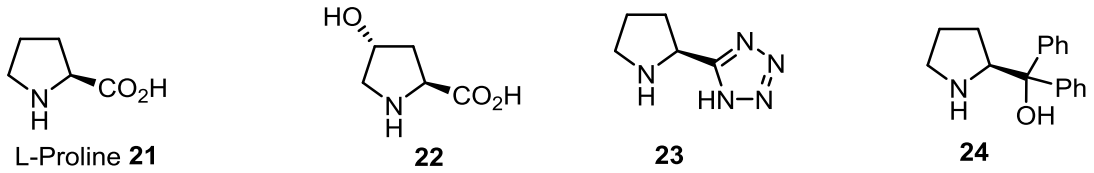
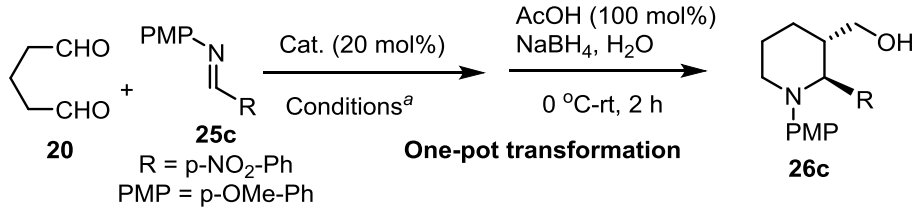


Figure 2.4 Catalysts screened for the organocatalytic Mannich reaction of glutaraldehyde with imines

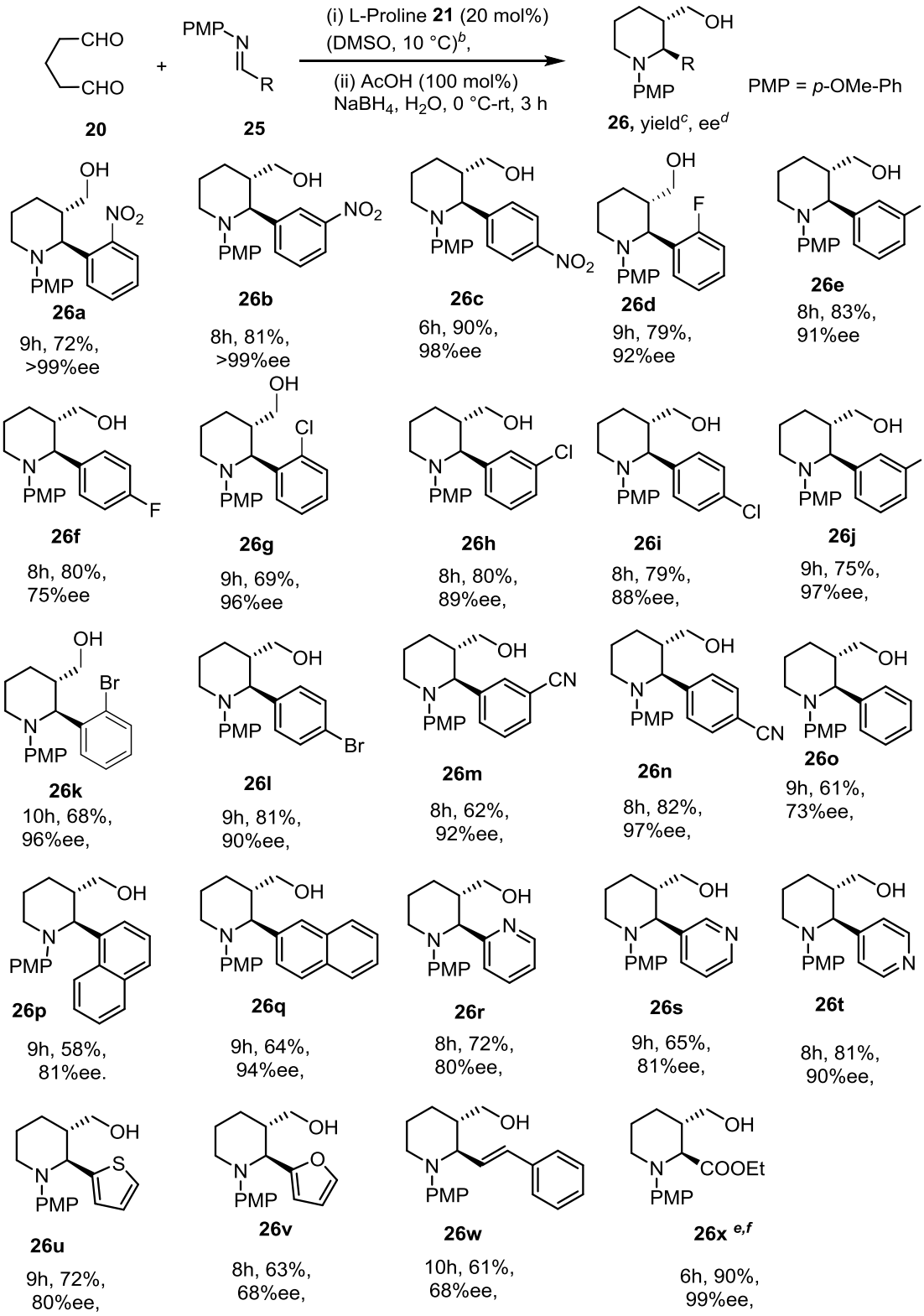
Table 2.1 Optimization of reaction conditions **26c**



Entry	Cat.	Conditionsa	Yield (%)[b]	dr[c]	ee (%)[d]
1	**21**	DMSO, rt, 4 h	81	>20:1	94
2	**22**	DMSO, rt, 5 h	72	>20:1	93
3	**23**	DMSO, rt, 7 h	65	>20:1	82
4	**24**	DMSO, rt, 10 h	n.r.	n.d.	n.d.
5	**21**	Toluene, rt, 12 h	n.r.	n.d.	n.d.
6	**21**	CH_3CN, rt, 8 h	58	10:1	90
7	**21**	THF, rt, 7 h	40	10:1	85
8	**21**	CH_2Cl_2, rt, 12 h	n.r.	n.d.	n.d.
9	**21**	1,4-dioxane, rt, 10 h	46	10:1	88
10	**21**	DMF, rt, 6 h	71	>20:1	92
11	**21**	NMP, rt, 5h	65	>20:1	95
12	**21**	DMSO, 10 °C, 6 h	90	>25:1	98
13	**21**	DMSO, 5 °C, 10 h	75	>25:1	98
14[e]	**21**	DMSO, 10 °C, 9 h	68	>25:1	96

[a](i) Imine **25c** (0.3 mmol), glutaraldehyde **20** (25% aqueous sol., 0.9 mmol), catalyst (20 mol%), solvent (3.0 mL) (ii) H_2O (2.0 mL). [b]Isolated yield refers to **25c** (after two steps in one pot operation). [c]Determined by ^{1}H-NMR. [d]Determined by HPLC analysis using CHIRALPAK-IA column using iPrOH/Hexane as solvents. [e]Catalyst 32 (10 mol%).

Table 2.2 Generality of formal [4+2] annulation for piperidine synthesis **26**



[a] (i) Imine **25** (0.3 mmol), **20** (25% aqueous sol., 0.9 mmol), **21** (20 mol%), DMSO (3.0 mL), (ii) H_2O (2.0 mL). [b] Time for Mannich reaction catalyzed by **32** (20 mol%). [c] Isolated yield refers to **25**. [d]Determined by HPLC analysis using CHIRALPAK-IA and IB columns using *i*-PrOH/Hexane as solvents. [e]Reaction was carried out without water. [f]Aldimine was prepared *in situ*.

Our initial experimentations showed that among the amine catalysts were screened (entry 1-4, **Table 2.1**), proline **21** efficiently catalyzed the direct Mannich reaction of aqueous glutaraldehyde **20** (25% sol.) with imine **25c**, which on acid catalyzed reductive cyclization afforded substituted piperidine **26c** with good yield and selectivity (entry 1, **Table 2.1**). Solvent screening (entry 5-11, **Table 2.1**) revealed that polar aprotic solvents were optimal for this one-pot transformations and particularly DMSO was preferred as a solvent. Gratifyingly, enhancement in the yield (90%) and enantioselectivity (98%) observed, when the reaction was carried out at 10 ^oC (entry 12, **Table 2.1**). Further decreasing the reaction temperature (entry 13, **Table 2.1**), and catalyst loading (entry 14, **Table 1**) led to the prolonged reaction with reduced yields. Thus, we preferred to perform this one-pot cascade sequence with optimized conditions (entry 12, **Table 2.1**).

With the optimal conditions in hand, we further explored the scope of proline **21** catalyzed asymmetric [4+2] annulation reaction with regard to a variety of preformed *N*-PMP aldimines **25** and the results are summarized in Table 2.2. In general, all the *N*-PMP aldimines derived from corresponding aromatic aldehydes worked well and provided a series of 2, 3-disubstituted piperidines **26** in moderate to high yields (up to 90%) with high diastereo- (>25:1) and excellent enantioselectivity (up to >99 % ee) under optimized conditions (**Table 2.2**). In case of electron-deficient aryl-imines, reactions preceded very well, **26a** – **26n** (**Table 2.2**).

However, the reactions were rather slow in cases of imines preformed from 2-substituted aldehydes for their corresponding products **26a, 26d, 26g, 26k** (**Table 2.2**), and naphthaldehydes piperidines **26p, 26q** (**Table 2.2**) lead to lower yields, possibly because of the steric crowding. In addition, imines derived from hetero-aromatic aldehydes also resulted the corresponding products in good yields and enantioselectivities which are **26r – 26v** (**Table 2.2**). In case of an alkenyl imine **25w**, derived from α-β-unsaturated aldehyde, the reaction proceeded with good yields and low enantioselectivity (**Table 2.2**). A clean transformation to highly functionalized

26x was observed with high yields (90%) and excellent selectivities (>25:1 dr, 99% ee), when activated imine **25x** was utilized without water (**Table 2.2**).

The relative stereochemistry of C2 and C3 as *trans*- and absolute stereochemistry as (2*S*, 3*S*) were confirmed through the coupling constant determination and comparing the $[\alpha]_D$ of one of our compounds **26o** with literature data i. e. $[\alpha]D^{25}$ = +2.6 (*c* 0.5, $CHCl_3$, 73% ee); Lit: $[\alpha]D^{25}$ = +3.5 (*c* 0.2, $CHCl_3$).[41] Single-crystal X-ray study of **26t** further confirmed the stereo chemical outcome, as expected through L-proline **21** catalyzed *syn*-Mannich reaction, followed by cyclization; stereochemistry of all other products were assigned through analogy.

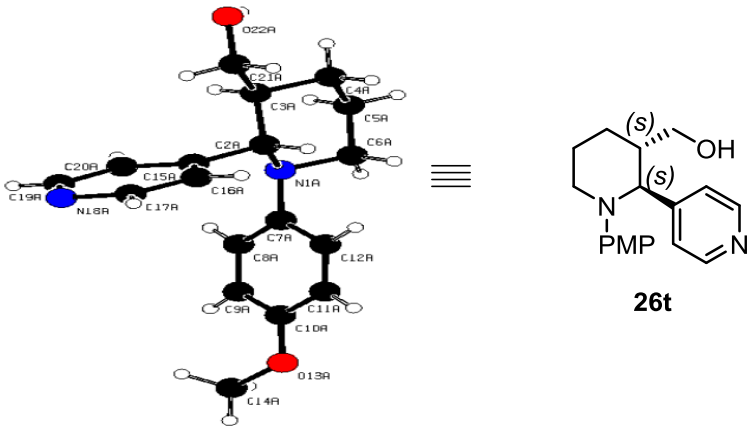
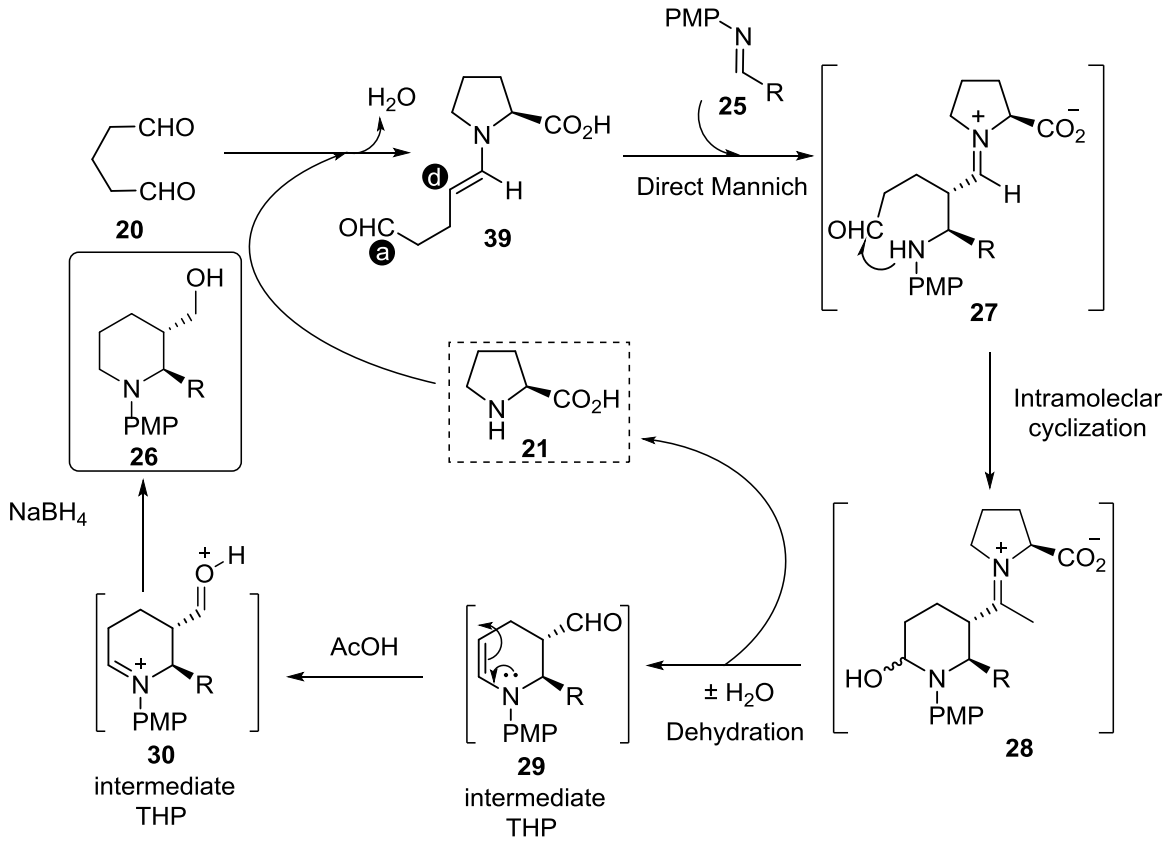
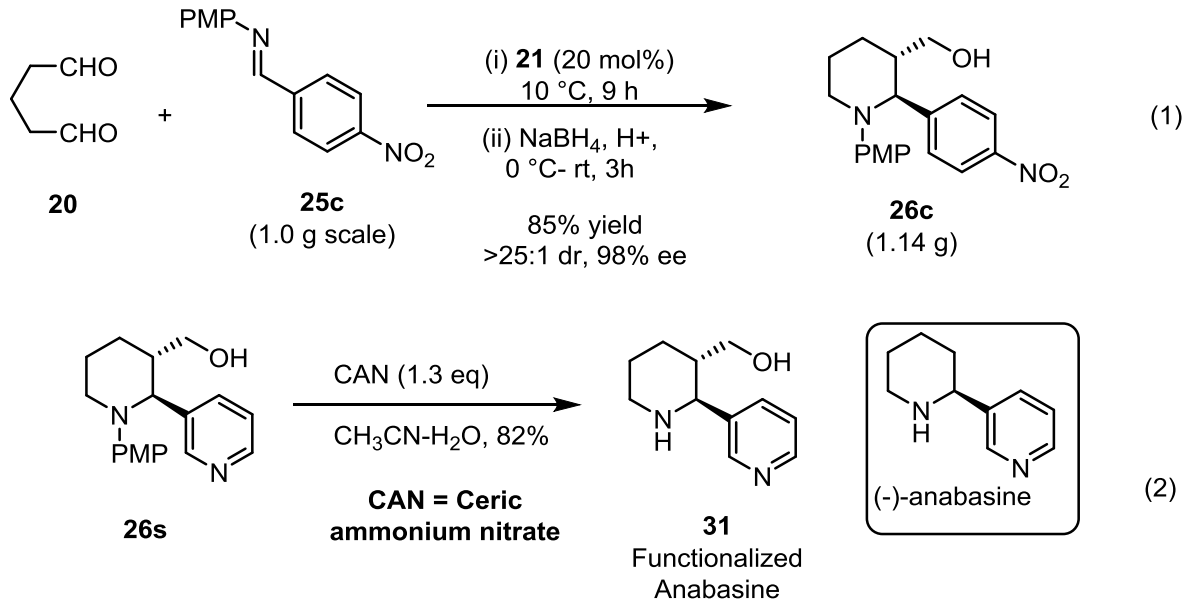


Figure 2.5 Absolute stereochemistry of one of the product **26t** through X-ray crystallography

To prove the concrete utility of our [4+2] annulation protocol, we inspected the reaction on a gram scale. While a somewhat longer reaction time was required, aldimine **25c** (1.0 g scale) could be transformed into **26c** (1.14 g) without much reduction in yields and with same selectivity (Eq. 1, **Scheme 2.9**). These substituted piperidines are resourceful building blocks in organic synthesis and can be readily converted into important products. For example; compounds **26s** contains the basic skeleton of anabasine, a tobacco alkaloid from *Nicotiana tobacum* known to possess nicotinic receptor agonist activity,[65, 66] was easily converted in to functionalized (–)-anabasine **27** (Eq. 2, **Scheme 2.9**). Plausible mechanism for the synthesis of enantioselective synthesis of piperidines proceeded through organocatalytic Mannich reaction of glutaraldehyde **20** followed by intramolecular cyclization of **27** and consequent dehydration of the intermediate **28** produced the enamine intermediate **29**. The acid mediated reduction of enamine intermediate **29** produced the functionalized piperidine **26** in the same pot as shown in **scheme 2.8.**



Scheme 2.8 Plausible mechanism for the synthesis of piperidines from glutaraldehyde and imine



Scheme 2.9 Application at gram-scale and synthesis of functionalized (–)-anabasine

2.4 Conclusion:

In conclusion of this chapter, we have developed an organocatalytic asymmetric two component direct synthesis of 2, 3-substituted piperidines. The present one-pot cascade sequence involves direct Mannich reaction of glutaraldehyde **20** with various *N*-PMP aldimines **25**, followed by acid catalyzed reductive cyclization, through 1,4-carbon *donor-acceptor* strategy as formal [4+2] cycloaddition under very mild conditions. The viability of method was established through; *i*) the reaction works efficiently at gram scale, and *ii*) one step synthesis of basic skeleton of (–)-anabasine alkaloid. The method described herein opens a wide and easy access to synthesize 2, 3-substituted piperidines of biological importance. Further applications this methodology utilizing aliphatic imines and synthesis of related alkaloids are currently under investigation in our laboratory and will be presented in due course.

2.5 General Experimental Methods:

All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on SiO_2 gel F-254 plates. The normal column chromatography was performed on silica gel (100-200 mesh) and Flash column chromatography was performed on silica gel (230-400 meshes) using the mixture of Hexane-EtOAc as the eluting solvent. All reagents were of analytical grade and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution and spectral data were reported in ppm relative to tetramethylsilane (TMS) as an internal standard. High-resolution mass spectra were recorded using the quadrupole electrospray ionization (ESI) technique. HPLC was performed on Water-2998 Instrument using CHIRALPAK-IA and IB columns and *i*-PrOH/Hexane as the solvent system.

2.6 General procedure for the organocatalytic Mannich-intramolecular reductive cyclization cascade as [4+2] annulation reaction:

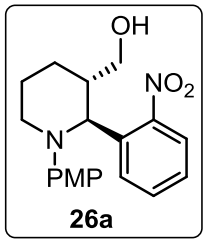
Glutaraldehyde solution **20** (25% in water, 0.30 mL, 0.9 mmol) was added to a mixture of preformed *N*-PMP aldimine **25** (0.3 mmol) and L-proline **21** (6.9 mg, 0.06 mmol) in DMSO (3.0 mL) at 10 ^{o}C. The reaction mixture was further stirred at the same temperature until the imine was consumed as monitored by TLC. Once the imine is over, the reaction was taken to 0 °C and cold water (2.0 mL), CH_3CO_2H (100 mol%, 18 μL) was added. To this reaction mixture, $NaBH_4$ was added cautiously at 0 °C, further stirred for 3 h and allows it come to room temperature. The reaction was subsequently quenched with $NaHCO_3$ solution (20 % sol, 10 mL). The aqueous

solution was extracted with ethyl acetate (2 × 10 mL) and combined organic extracts were washed with brine once, dried over anhydrous Na_2SO_4 and concentrated in a vacuum after filtration. The residue was purified by column chromatography on silica gel (Hexane: EtOAc) to afford *trans*-2,3-disubstituted piperidine **26** with 57-90% yields.

The enantiomeric excess (*ee*) of the products was determined by HPLC analysis using CHIRALPAK-IA and IB columns. The relative and absolute configuration was established through the comparison of optical rotation with known compound as well as by the single crystal X-ray of **26t**. The ORTP-diagram of X-ray structure was chosen for refinement has C2-(*S*), and C3-(*S*) stereochemistry, as expected through the well documented *syn*-selective direct Mannich reaction catalyzed by L-proline **21**.

2.7 Analytical data

((2*S*,3*S*)-1-(4-Methoxyphenyl)-2-(2-nitrophenyl)piperidin-3-yl)methanol (26a):

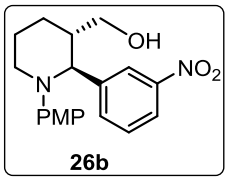


26a

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58-1.64 (m, 1H), 1.86-1.94 (m, 3H), 2.01-2.04 (m, 1H), 2.78 (dt, *J* = 3.5 Hz, 11.6 Hz, 1H), 3.20 (d, *J* = 11.7 Hz, 1H), 3.34-3.42 (m, 2H), 3.65 (s, 3H), 4.46 (d, *J* = 9.6 Hz, 1H), 6.60 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* =8.9 Hz, 2H), 7.17 (t, *J* = 7.2 Hz, 1H), 7.41 (t, *J* = 8.1 Hz, 1H), 7.49 (d, *J* = 8.1 Hz, 1H) 7.81 (d, *J* = 8.0 Hz, 1H); ^{13}C-NMR $CDCl_3$) δ 25.81, 27.50, 47.22, 55.16, 57.85, 60.92, 64.43, 113.91 (2C), 123.26, 125.92 (2C), 127.46, 130.52, 132.49, 137.11, 145.56, 150.82, 156.15; HRMS (ESI): Calcd. for $C_{19}H_{22}N_2O_4$ (MH^+) 343.1658, Found 343.1649. $[\alpha]_D^{25}$ = + 41.2 (*c* 0.5, $CHCl_3$, > 99% ee),

Enantiomeric excess was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 18.108 min, major enantiomer t_R = 19.477 min.

((2*S*, 3*S*)-1-(4-Methoxyphenyl)-2-(3-nitrophenyl)piperidin-3-yl)methanol (26b):



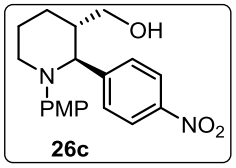
26b

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53-1.60 (m, 2H), 1.87-1.91 (m, 2H), 1.97-2.02 (m, 1H), 2.84 (dt, *J* = 3.6 Hz, 11.2 Hz, 1H), 3.27 (dd, *J* = 5.0 Hz , 10.7 Hz, 2H), 3.42 (dd, *J* = 3.5 Hz, 10.7 Hz , 1H), 3.65 (s, 3H), 4.04 (d, *J* = 9.1 Hz, 1H), 6.62 (d, *J* = 8.6 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 7.92 (d, *J* = 8.2 Hz, 1H), 8.15 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 25.48, 27.23, 45.86, 55.17, 56.94, 64.39, 66.11, 113.91 (2C), 121.83, 123.35, 125.57 (2C), 128.72, 134.78, 144.83, 145.39,

148.06, 155.68; HRMS (ESI): Calcd for $C_{19}H_{22}N_2O_4$ (MH^+) 343.1658, Found 343.1657. $[\alpha]_D^{25}$ = + 8.7 (*c* 1.0, $CHCl_3$, > 99% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 20.376 min, major enantiomer t_R = 21.716 min.

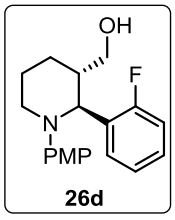
((2*S*, 3*S*)-1-(4-Methoxyphenyl)-2-(4-nitrophenyl)piperidin-3-yl)methanol (26c):



26c

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43-1.50 (m, 1H), 1.77-1.83 (m, 3H), 1.87-1.91 (m, 1H), 2.75 (dt, *J* = 3.5 Hz, 11.6 Hz, 1H), 3.13-3.19 (m, 2H), 3.30 (dd, *J* = 3.5 Hz, 10.7 Hz, 1H), 3.56 (s, 3H), 3.96 (d, *J* = 9.1 Hz, 1H), 6.53 (d, *J* = 8.9 Hz, 2H), 6.81 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 7.89 (d, *J* = 8.7 Hz, 2H); ^{13}C-NMR ($CDCl_3$) δ 25.38, 27.10, 45.79, 55.11, 56.79, 64.17, 66.08, 113.86 (2C), 123.08 (2C), 125.24 (2C), 129.26 (2C), 145.39, 146.51, 150.51, 155.58; HRMS (ESI): Calcd for $C_{19}H_{22}N_2O_4$ (MH^+) 343.1659, Found 343.1659. $[\alpha]_D^{25}$ = +18.2 (*c* 0.5, $CHCl_3$, 98% ee); Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 25.343 min, major enantiomer t_R = 35.604 min.

((2*S*, 3*S*)-2-(2-fluorophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26d):

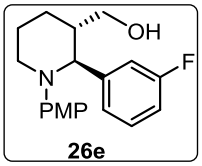


26d

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48-1.55 (m, 1H), 1.84-1.95 (m, 3H), 2.03-2.07 (m, 1H), 2.78 (dt, *J* = 3.3 Hz, 11.6 Hz, 1H), 3.29-3.42 (m, 3H), 3.65 (s, 3H), 4.18 (d, *J* = 9.7 Hz, 1H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.84 (t, *J* = 8.6 Hz, 1H), 6.92 (m, 1H), 6.94 (d, J = 9.0 Hz, 2H), 7.00-7.06 (m, 1H), 7.42 (dt, 1.7 Hz, 7.5 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 25.78, 27.64, 46.23, 55.11, 58.10, 58.39, 64,85, 113.68 (2C), 114.38, 114.57, 124.23, 125.17 (2C), 128.02, 129.43, 130.84, 148.99, 155.60; HRMS (ESI): Calcd for $C_{19}H_{22}FNO_2$ (MH^+) 316.1714, Found 316.1715. $[\alpha]_D^{25}$ = + 33.20 (*c* 0.5, $CHCl_3$, 92% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 16.282 min, major enantiomer t_R = 17.811 min.

((2*S*, 3*S*)-2-(3-fluorophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26e):



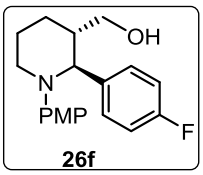
26e

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 1H), 1.52 (bs, -OH, 1H), 1.83-1.87 (m, 3H), 1.94-1.99 (m, 1H), 2.83 (dt, *J* = 3.8 Hz, 11.6 Hz, 1H), 3.22-3.30 (m, 2H), 3.42 (dd, *J* = 4.2 Hz, 10.8 Hz, 1H), 3.66 (s, 3H), 3.87 (d, *J* = 8.9 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 2H), 6.73-6.77 (m, 1H), 6.90 (d, *J* = 8.9 Hz, 2H), 6.99 (m, 2H), 7.01-7.11 (m, 1H); ^{13}C NMR ($CDCl_3$); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.42, 27.22, 45.81, 55.22, 56.60, 65.81,

66,56, 113.51, 113.77 (2C), 115.07, 115.28, 124.25, 125.11 (2C), 129.24, 129.32, 145.82, 155.36; HRMS (ESI): Calcd for $C_{19}H_{22}FNO_2$ (MH^+) 316.1714, Found 316.1710. $[\alpha]_D^{25}$ = +11.10 (*c* 1.0, $CHCl_3$, 91% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 14.376 min, major enantiomer t_R 16.556 min.

((2*S*, 3*S*)-2-(4-fluorophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26f):

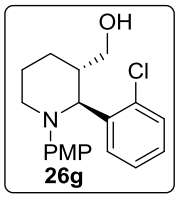


26f

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48-1.53 (m, 1H), 1.82-1.91 (m, 3H), 1.96-2.01 (m, 1H), 2.83 (dt, *J* = 3.7 Hz, 11.5 Hz, 1H), 3.22-3.28 (m, 2H), 3.40 (dd, *J* = 4.1 Hz, 10.8 Hz, 1H), 3.66 (s, 4H), 3.81 (d, *J* = 9.1 Hz, 1H), 6.62 (d, *J* = 8.9 Hz, 2H), 6.82 (t, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 7.19 (dd, *J* = 5.7 Hz, 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.50, 27.38, 45.88, 55.14, 56.80, 64.84, 66.58, 113.64 (2C), 114.66, 114.83, 125.39 (2C), 129.80, 129.86, 137.81, 145.81, 155.36, 160.37; HRMS (ESI): Calcd for $C_{19}H_{22}FNO_2$ (MH^+) 316.1714, Found 316.1721. $[\alpha]_D^{25}$ = + 9.1 (*c* 1.0, $CHCl_3$,75% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 94:06), 0.5 mL/min; minor enantiomer t_R = 21.161 min, major enantiomer t_R = 26.494 min.

((2*S*, 3*S*)-2-(2-chlorophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26g):

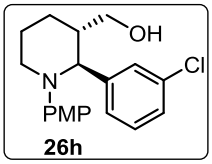


26g

^{1}H NMR (400 MHz, CDCl3) δ 1.49-1.56 (m, 1H), 1.80-1.95 (m, 3H), 2.04-2.08 (m,1H), 2.78 (dt, *J* = 3.3 Hz, 11.6 Hz, 1H), 3.29-3.41 (m, 3H), 3.65 (s, 3H), 4.32 (d, *J* = 9.7 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 2H), 6.94-6.99 (m, 3H), 7.07 (t, *J* = 7.8 Hz, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 1.6 Hz, 7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.88, 27.67, 47.47, 55.13, 58.28, 61.92, 64.55, 113.67 (2C), 125.40 (2C), 127.05, 127.74, 128.60, 129.96, 133.74, 140.19, 145.96, 155.65; HRMS (ESI): Calcd for $C_{19}H_{22}ClNO_2$ (MH^+) 332.1417, Found: 332.1419. $[\alpha]_D^{25}$ = + 74.00 (*c* 0.5, $CHCl_3$, 96% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 13.442 min, major enantiomer t_R = 16.753 min.

((2*S*, 3*S*)-2-(3-chlorophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26h):



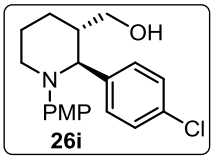
26h

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42-1.48 (m, 1H), 1.81-1.86 (m, 3H), 1.93-1.98 (m, 1H), 2.83 (dt, *J* = 4.0 Hz, 11.7 Hz, 1H), 3.20-3.28 (m, 2H), 3.38 (dd, *J* = 4.0 Hz, 10.8 Hz, 1H), 3.63 (s, 3H), 3.85 (d, *J* = 8.8 Hz, 1H), 6.62 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.01-7.05 (m, 2H), 7.08-7.10 (m, 1H), 7.26 (s, 1H); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 25.29, 27.08, 45.63, 55.10, 56.40, 64.56, 66.29, 113.74 (2C), 125.00 (2C), 126.72, 126.78, 128.34, 129.07, 133.78, 144.47, 145.66, 155.28; HRMS (ESI): Calcd for $C_{19}H_{22}ClNO_2$ (MH^+) 332.1417, Found: 332.1415. $[\alpha]_D^{25}$ = + 6.0 (*c* 1.0, $CHCl_3$, 89% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 14.141 min, major enantiomer t_R = 15.436 min.

((2*S*, 3*S*)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26i):

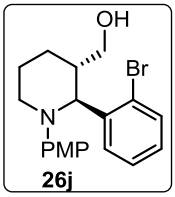


26i

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41-1.49 (m, 1H), 1.79-1.87 (m, 3H), 1.94-1.98 (m, 1H), 2.82 (dt, *J* = 3.4 Hz, 10.4 Hz, 1H), 3.21-3.25 (m, 2H), 3.37 (dd, *J* = 4.0 Hz, 10.7 Hz, 1H) 3.64 (s, 3H), 3.83 (d, *J* = 9.0 Hz, 1H), 6.62 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.36, 27.19, 45.66, 55.05, 56.68, 64.56, 66.29, 113.67 (2C), 125.13 (2C), 128.02 (2C), 129.71 (2C), 131.97, 140.68, 145.64, 155.30; HRMS (ESI): Calcd for $C_{19}H_{22}ClNO_2$ (MH^+) 332.1417, Found: 332.1416. $[\alpha]_D^{25}$ = + 10.4 (*c* 0.5, $CHCl_3$, 88% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 15.440 min, major enantiomer t_R = 19.712 min.

((2*S*, 3*S*)-2-(2-bromophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26j):

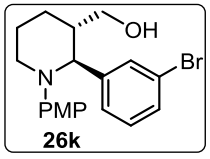


26j

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50-1.57 (m, 1H), 1.81-1.93 (m, 3H), 2.04-2.07 (m, 1H), 2.79 (dt, *J* = 3.3 Hz, 11.7 Hz, 1H), 3.29 (d, *J* = 11.7 Hz, 1H), 3.39 (d, *J* = 5.4 Hz, 1H), 3.66 (s, 3H), 4.26 (d, *J* = 9.6 Hz, 1H), 6.63 (d, *J* = 8.9 Hz, 2H), 6.90 (dt, *J* = 1.7 Hz, 7.5 Hz, 1H), 6.97 (d, *J* = 8.8 Hz, 2H), 7.12 (t, *J* = 7.1 Hz, 1H), 7.33 (dd, *J* = 1.1 Hz, 8.0 Hz, 1H), 7.53 (dd, *J* = 1.7 Hz, 7.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.89, 27.62, 47.73, 55.15, 58.17, 64.53, 64.75, 113.66 (2C), 124.81, 125.70 (2C), 127.63, 128.14, 130.43, 131.94, 141.78, 148.90, 155.73; HRMS (ESI): Calcd for $C_{19}H_{22}BrNO_2$ (MH^+) 376.0912, Found 376.0914. $[\alpha]_D^{25}$ = + 61.0 (*c* 0.5, CHCl3, 96% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH = 84:16), 0.5 mL/min; minor enantiomer t_R = 16.358 min, major enantiomer t_R = 21.195 min.

((2*S*, 3*S*)-2-(3-bromophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26k):



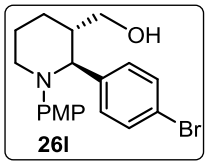
26k

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45-1.52 (m, 1H), 1.82-1.89 (m, 3H), 1.95-2.00 (m, 1H), 2.81-2.87 (dt, *J* = 3.3 Hz, 11.6 Hz, 1H), 3.22-3.31 (m, 2H), 3.43 (dd, *J* = 4.0 Hz, 10.8 Hz, 1H), 3.67 (s, 3H), 3.85 (d, *J* = 8.9 Hz, 1H), 6.64 (d, *J*

= 8.9 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.99 (t, *J* =7.8 Hz, 1H), 7.15 (d, *J* = 7.7 Hz, 1H), 7.16-7.20 (m, 1H),7.43 (t, *J* = 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.35, 27.14, 45.74, 55.21, 56.46, 64.74, 66.35, 113.82 (2C), 122.18, 125.07 (2C), 127.23, 129.45, 129.77, 131.31, 144.81, 145.71, 155.38; HRMS (ESI): Calcd for $C_{19}H_{22}BrNO_2$ (MH^+) 376.0912, Found 376.0910. $[\alpha]_D^{25}$ = – 10.0 (*c* 0.5, $CHCl_3$, 97% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 14.346 min, major enantiomer t_R = 15.340 min.

((2*S*, 3*S*)-2-(4-bromophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26l):

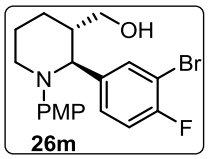


26l

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47-1.54 (m, 1H), 1.83-1.89 (m, 3H), 1.98-2.02 (m, 1H), 2.85 (dt, *J* = 4.0 Hz, 10.4 Hz, 1H), 3.24-3.30 (m, 2H), 3.42 (dd, *J* = 4.0 Hz, 10.8 Hz, 1H), 3.69 (s, 3H), 3.85 (d, *J* = 9.1 Hz, 1H), 6.66 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H) 7.28 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.43, 27.25, 40.79, 55.18, 56.69, 64.76, 66.41, 113.78 (2C), 125.18 (2C), 128.52 , 130.16 (2C), 131.06 (2C), 141.32, 145.75, 155.39; HRMS (ESI): Calcd for $C_{19}H_{22}BrNO_2$ (MH^+) 376.0913, Found 376.0909. $[\alpha]_D^{25}$ = – 6.4 (*c* 1.0, $CHCl_3$, 90% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 16.002 min, major enantiomer t_R = 21.944 min.

((2*S*, 3*S*)-2-(3-bromo-4-fluorophenyl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26m):

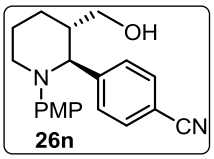


26m

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.79-1.88 (m, 4H), 1.95-1.99 (m, 1H), 2.83 (dt, *J* = 4.1 Hz, 11.6 Hz, 1H), 3.20-3.27 (m, 2H), 3.40 (dd, *J* = 3.8 Hz, 10.7 Hz, 1H), 3.67 (s, 3H), 3.84 (d, *J* = 9.1 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 2H), 6.85 (m, 1H), 6.89. (d, *J* = 9.0 Hz, 2H), 7.11-7.14 (m, 1H), 7.47 (dd, *J* = 2.1 Hz, 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.37, 27.15, 45.78, 55.17, 56.63, 64.46, 65.71, 113.85 (2C), 115.58, 115.80, 125.27 (2C), 128.90, 133.10, 139.82, 145.54, 155.53, 158.70; HRMS (ESI): Calcd for $C_{19}H_{21}BrFNO_2$(MH^+) 394.0818, Found 394.0821. $[\alpha]_D^{25}$ = – 6.2 (*c* 1.0, $CHCl_3$, 92% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 14.096 min, major enantiomer t_R = 15.592 min.

4-((2*S*, 3*S*)-3-(hydroxymethyl)-1-(4-methoxyphenyl)piperidin-2-yl)benzonitrile (26n):

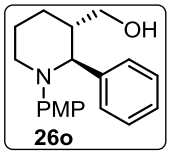


26n

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49- 1.56 (m, 1H), 1.80-1.86 (m, 3H), 1.94-1.98 (m, 1H), 2.82 (dt, *J* = 4.2 Hz, 10.4 Hz, 1H), 3.19-3.25 (m, 2H), 3.35 (dd, *J* = 3.7 Hz, 10.7 Hz, 1H), 3.64 (s, 3H), 3.97 (d, *J* = 9.1 Hz, 1H), 6.61 (d, *J* = 9.0 Hz, 2H), 6.87 (d, *J* = 9.0, 2H), 7.38 (q, *J* = 8.6 Hz, 12.2 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.31, 27.03, 45.61, 55.12, 56.59, 64.16, 66.27, 110.12, 113.81 (2C), 118.82, 125.11 (2C), 129.22 (2C), 131.66 (2C), 145.40, 148.27, 155.48; HRMS (ESI): Calcd for $C_{20}H_{22}N_2O_2$ (MH^+) 323.1759, Found 323.1763. $[\alpha]_D^{25}$ = + 8.8 (*c* 1.0, CHCl3, 97% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 24.835 min, major enantiomer t_R = 34.001 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-phenylpiperidin-3-yl)methanol (26o):

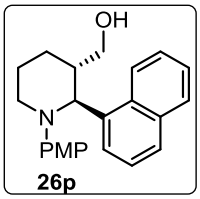


26o

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85-1.89 (m, 2H), 1.94-2.06 (m, 3H), 2.85 (dt, *J* = 3.5 Hz, 11.7 Hz, 1H), 3.24-3.32 (m, 2H), 3.45 (dd, *J* = 4.4 Hz, 11.0 Hz, 1H), 3.66 (s, 3H), 3.84 (d, *J* = 8.6 Hz, 1H), 6.62 (d, *J* = 9 .0 Hz, 2H), 6.91 (d, *J* = 9.4 Hz, 2H), 7.08 (d, *J* = 7.2 Hz, 1H), 7.15 (t, *J* = 7.2 Hz, 2H), 7.24 (d, *J* = 7.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.51, 27.42, 45.96, 55.18, 56.60, 65.27, 67.46, 113.66 (2C), 125.11 (2C), 126.72 ,128.02 (2C) ,128.47 (2C), 142.13, 146.05, 155.21; HRMS (ESI): Calcd for $C_{19}H_{23}NO_2$ (MH+) 298.1807, Found: 298.1811. $[\alpha]_D^{25}$ = + 2.6 (*c* 0.5, $CHCl_3$, 73% ee); Lit: $[\alpha]_D^{25}$ = + 3.5 (*c* 0.2, $CHCl_3$).*Ref 67.*

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R =29.181 min, major enantiomer t_R = 23.841 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(naphthalen-1-yl)piperidin-3-yl)methanol (26p):



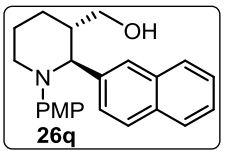
26p

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45-1.56 (m, 1H), 1.84-1.90 (m, 1H), 1.95-2.07 (m, 2H), 2.18-2.27 (m, 1H), 2.85-2.94 (m, 1H), 3.13 (dd, *J* = 5.4 Hz, 5.6 Hz, 1H), 3.23 (dd, 4.3 Hz, 4.3 Hz, 1H), 3.38 (d, *J* = 12.7 Hz, 1H), 3.51 (s, 3H), 4.50 (d, *J* = 9.2 Hz, 1H), 6.45 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.23 (d, *J* = 7.7 Hz, 1H), 7.37-7.51 (m, 4H), 7.55 (d, *J* = 8.2 Hz, 1H), 7.72 (d, *J* = 8.2 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.78, 27.82, 45.70, 55.00, 57.98, 63.53, 65.15, 113.47 (2C), 124.40, 124.97, 125.08, 125.16, 125.40, 126.96, 127.34, 128.70, 129.49, 131.81, 133.68, 138.10, 146.03, 155.19;

HRMS (ESI): Calcd for $C_{23}H_{25}NO_2$ (MH^+): 348.1963, Found 348.1967. $[\alpha]_D^{25}$ = + 34.4 (*c* 0.5, $CHCl_3$, 81% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 16.925 min, major enantiomer t_R = 18.265 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(naphthalen-2-yl)piperidin-3-yl)methanol (26q):

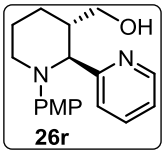


26q

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.50-1.57 (m, 1H), 1.86-1.94 (m, 2H), 2.00-2.08 (m, 2H), 2.93 (dt, *J* = 3.4 Hz, 11.6 Hz, 1H), 3.28-3.35 (m, 2H), 3.40 (dd, *J* = 4.1 Hz, 10.9 Hz, 1H), 3.59 (s, 3H), 4.04 (d, *J* = 8.7 Hz, 1H), 6.60 (d, *J* = 9.0 Hz, 2H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.38-7.43 (m, 2H), 7.51 (dd, *J* = 6.9 Hz, 8.4 Hz, 1H), 7.65-7.74 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.47, 27.32, 45.63, 55.03, 56.70, 64.96, 67.22, 113.67 (2C), 125.06, 125.11, 125.31, 125.60, 126.37, 127.34, 127.44, 127.64, 127.69, 132.51, 133.03, 139.76, 145.94, 155.16; HRMS (ESI): Calcd for $C_{23}H_{25}NO_2$ (MH^+): 348.1963, Found 348.1959. $[\alpha]_D^{25}$ = + 9.5 (*c* 1.0, $CHCl_3$, 94% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 18.405 min, major enantiomer t_R = 23.997 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(pyridin-2-yl)piperidin-3-yl)methanol (26r):

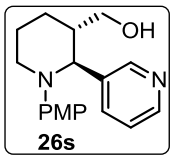


26r

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66-1.73 (m, 1H), 1.84-1.87 (m, 4H), 2.81-2.87 (m, 1H), 3.27 (dd, *J* = 4.4 Hz, 11.6 Hz, 1H), 3.34-3.42 (m, 2H), 3.65 (s, 3H), 4.24 (d, *J* = 8.8 Hz, 1H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.97-7.01 (m, 1H), 7.28 (d, *J* = 7.9 Hz, 1H), 7.44 (dt, *J* = 1.6 Hz, 7.7 Hz, 1H) 8.38 (d, *J* = 4.8 Hz 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.40, 27.32, 45.74, 55.21, 56.40, 64.66, 67.30, 113.87 (2C), 121.68, 122.61, 123.91 (2C), 136.60, 146.04, 147.97, 154.88, 162.55; HRMS (ESI): Calcd for C18H22N2O2 (MH^+) 299.1759 , Found: 299.1757. $[\alpha]_D^{25}$ = + 32.4 (*c* 0.5, $CHCl_3$, 80% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 0.5mL/min; major enantiomer t_R = 42.928 min, minor enantiomer t_R = 48.704 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(pyridin-3-yl)piperidin-3-yl)methanol (26s):



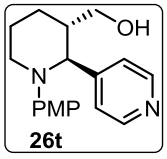
26s

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54-1.60 (m, 2H), 1.81-1.89 (m, 3H), 2.82 (dt, *J* = 4.0 Hz, 10. 4 Hz, 1H), 3.21-3.25 (m, 2H), 3.38 (dd, *J* = 3.6 Hz, 11.7 Hz, 1H), 3.64 (s, 3H), 3.94 (d, *J* = 9.2 Hz, 1H), 6.60 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.06 (dd, *J* = 4.8 Hz, 11.8 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 8.23 (dd, *J* = 1.6 Hz, 4.7

Hz, 1H) 8.39 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.54, 27.31, 40.80, 45.75, 55.18, 62.53, 64.33, 113.89 (2C), 123.26, 123.49, 125.53 (2C), 145.51, 148.26, 148.46, 149.82, 155.62; HRMS (ESI): Calcd for $C_{18}H_{22}N_2O_2$ (MH^+) 299.1759, Found: 299.1764. $[\alpha]_D^{25}$ = + 11.1 (*c* 1.0, MeOH, 81% ee);

Enantiomeric excess was determined by HPLC with a Chiral pak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5mL/min; major enantiomer t_R = 46.112 min, minor enantiomer t_R = 52.412 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(pyridin-4-yl)piperidin-3-yl)methanol (26t):

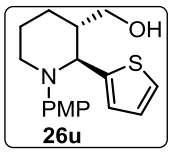


26t

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.52-1.58 (m, 2H), 1.81-1.86 (m, 3H), 2.84-2.90 (m, 1H), 3.21-3.25 (m, 2H), 3.40 (dd, *J* = 3.9 Hz, 10.7 Hz, 1H), 3.65 (s, 3H), 4.03 (d, *J* = 8.6 Hz, 1H), 6.63 (d, *J* = 9.0 Hz, 2H), 6.88 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 6.0 Hz, 2H), 8.29 (d, *J* = 6.0 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 24.82, 26.42, 40.37, 44.89, 55.61, 61.88, 64.76, 113.68 (2C), 123.80 (2C), 124.23 (2C), 145.29, 148.46 (2C), 152.30, 154.98; HRMS (ESI): Calcd for $C_{18}H_{22}N_2O_2$ (MH^+) 299.1759, Found: 299.1762. $[\alpha]_D^{25}$ = + 12.4 (*c* 1.0, $CHCl_3$, 90% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 85:15), 0.5 mL/min; minor enantiomer t_R = 16.558 min, major enantiomer t_R = 18.641 min.

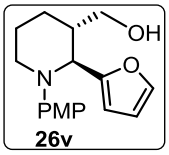
((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(thiophen-2-yl)piperidin-3-yl)methanol (26u):



26u

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.54-1.59 (m, 1H), 1.76-1.84 (m, 3H), 1.97-2.03 (m, 1H), 2.07-2.12 (m, 1H), 2.97-3.07 (m, 1H), 3.19-3.25 (m, 1H), 3.58 (dd, *J* = 5.2 Hz, 10.6 Hz, 1H), 3.72 (s, 3H), 4.56 (d, *J* = 6.5 Hz, 1H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.75 (d, *J* = 3.7 Hz, 1H), 6.78 (dd, 3.5 Hz, 5.0 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 7.09 (dd, 1.1 Hz, *J* = 5.0 Hz 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.42, 28.91, 44.97, 51.93, 55.33, 61.44, 65.23, 113.96 (2C), 122.81 (2C), 124.20, 125.64, 125.83, 130.86, 145.57, 154.72; HRMS (ESI): Calcd for $C_{17}H_{21}NO_2S$ (MH^+) 304.1371, Found. 304.1375. $[\alpha]_D^{25}$ = – 5.2 (*c* 1.0, $CHCl_3$, 80% ee);
Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 19.560 min, minor enantiomer t_R = 23.400 min.

((2*S*, 3*S*)-2-(fuyan-2-yl)-1-(4-methoxyphenyl)piperidin-3-yl)methanol (26v):



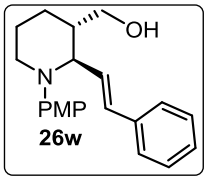
26v

^{1}H NMR (300 MHz, $CDCl_3$) δ 1.52-1.60 (m, 1H), 1.71-1.79 (m, 1H), 1.81-1.86 (m, 1H), 1.91-1.98 (m, 1H), 2.23-2.30 (m, 1H), 3.02-3.08 (m, 1H), 3.15-3.20 (m, 1H), 3.60 (dd, *J* = 5.3 Hz, 10.7 Hz, 1H), 3.73 (s, 3H), 3.75 (dd, *J* = 6 Hz, 10.7

Hz, 1H,), 4.38 (d, *J* = 6.8 Hz, 1H), 5.91 (d, *J* = 3.2 Hz, 1H), 6.17 (dd, *J* = 1.8 Hz, 3.2 Hz, 1H), 6.74 (d, *J* = 9.0 Hz, 2H) 6.90 (d, *J* = 9.0 Hz, 2H), 7.27 (dd, *J* = 0.9 Hz, 1.9 Hz, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.59, 24.83, 41.33, 50.17, 55.38, 59.55, 65.17, 107.99, 109.87, 114.00 (2C), 121.70 (2C), 141.00, 145.68, 154.26, 154.55; HRMS (ESI): Calcd for $C_{17}H_{21}NO_3$ (MH^+): 288.1599, Found. 288.1595. $[\alpha]_D^{25} = -41.6$ (*c* 0.5, $CHCl_3$, 68% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 18.401 min, minor enantiomer t_R = 22.956 min.

((2*R*, 3*S*)-1-(4-methoxyphenyl)-2-((*E*)-styryl)piperidin-3-yl)methanol (26w):

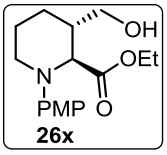


26w

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.54-1.65 (m, 1H), 1.81-1.88 (m, 2H), 1.92-2.01 (m, 2H), 3.00-3.08 (m, 1H), 3.19-3.24 (m, 1H), 3.76 (s, 3H), 3.80 (dd, *J* = 5.3 Hz, 10.7 Hz, 1H), 3.93 (dd, *J* = 5.5 Hz, 10.7 Hz, 1H) 3.97 (dd, *J* = 5.3 Hz, 7.3 Hz, 1H), 6.21 (dd, *J* = 7.3 Hz, 16.2 Hz, 1H), 6.34 (d, *J* = 16.3 Hz, 1H), 6.81 (d, *J* = 9.0 Hz, 2H), 7.00 (d, *J* = 9.0 Hz, 2H), 7.18-7.23 (m, 1H), 7.25-7.29 (m, 4H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 23.64, 24.37, 41.95, 49.58, 55.40, 63.55, 65.62, 114.12 (2C), 122.29 (2C), 126.16 (2C), 127.25, 128.39 (2C), 129.46, 132.13, 136.99, 145.55, 154.54; HRMS (ESI): Calcd for $C_{21}H_{25}NO_2$ (MH^+) 324.1963, Found 324.1967. $[\alpha]_D^{25} = -28.0$ (*c* 0.5, $CHCl_3$, 68% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 23.015 min, minor enantiomer t_R = 28.844 min.

((2*S*, 3*S*)-ethyl 3-(hydroxymethyl)-1-(4-methoxyphenyl)piperidine-2-carboxylate (26x):



26x

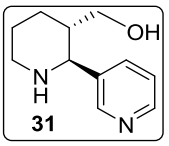
^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, J = 71. Hz, 1H), 1.54-1.59 (m, 1H), 1.64-1.73 (m, 2H), 2.26- 2.30 (m, 1H), 3.07-3.12 (m, 1H), 3.33-3.39 (m, 1H), 3.71 (dd, *J* = 5.3 Hz, 10.6 Hz, 1H), 3.73 (s, 3H), 3.88 (dd, *J* = 7.8 Hz, 10.6 Hz, 1H), 4.04 (dq, *J* = 2.8 Hz, 7.2 Hz, 14.1 Hz, 2H), 4.22 (d, *J* = 6.1 Hz, 1H), 6.78 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 9.0 Hz, 2H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 14.06, 21.98, 23.36, 39.26, 47.90, 55.36, 60.40, 62.59, 63.88, 114.15 (2C), 119.82 (2C), 145.57, 153.86, 172.97; HRMS (ESI): Calcd for $C_{16}H_{23}NO_4$ (MH^+) 294.1705, Found 294.1701. $[\alpha]_D^{25} = +27.4$ (*c* 0.5, $CHCl_3$, 99% ee);

Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; major enantiomer t_R = 20.197 min, major enantiomer t_R = 23.325 min.

2.8 Procedure for the preparation of functionalized anabasin 31:

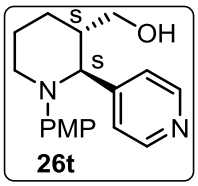
Compounds **26s** (0.045 g, 0.15 mmol) solution in CH_3CN (2 mL) was added slowly to the stirred solution of Ceric Ammonium Nitrate (CAN, 0.208 g, 0.38 mmol) in distilled water (2.0 mL) at 0 °C. The total reaction mixture was further stirred at same temperature for about 3 h, till the reaction complete by TLC. The reaction was quenched by adding the $NaHCO_3$ solution to bring the pH 10 and extracted with EtOAc (5 × 4 mL). The combined organic layer was washed with brine solution, dried over Na_2SO_4 and evaporated under reduced pressure. The crude material was passed through a small pad of column by eluting Hexane/acetone (70:30 to 40:60 ratio), to gave 0.023 g, 82% yield.

((2*S*, 3*S*)-(pyridin-3-yl)piperidin-3-yl)methanol (31):



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.5-1.68 (m, 5H), 2.18 (s, 1H, NH), 2.35-2.39 (m, 2H), 3.37-3.40 (m, 2H), 3.77 (s, 1H, OH), 4.08 (d, *J* = 8.7 Hz, 1H), 7.30 (dd, *J* = 4.9 Hz, 11.8 Hz, 1H), 7.74 (d, *J* = 7.9 Hz, 1H), 8.52 (d, *J* = 3.6 Hz, 1H) 8.59 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 25.72, 27.64, 42.87, 46.06, 64.98, 67.62, 136.92, 146.36 148.29, 153.65, 155.20; HRMS (ESI): Calcd. for $C_{11}H_{16}N_2O$ (MH^+) 193.1341, Found: 193.1345. $[\alpha]_D^{25}$ = + 9.2 (*c* 1.0, MeOH).

2.9 Crystal structure of (26t): [CCDC No. - 930264]



The titled compound, ((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(pyridin-4-yl)piperidin-3-yl)methanol, $C_{18}H_{22}N_2O_2$, crystallizes in the monoclinic space group P21 with the following unit-cell parameters: a = 9.1775(2), b = 10.7628(2), c = 16.9499 (5) Å, β = 107.577(2)^o, Z = 4. The asymmetric unit of the title compound contains two independent molecules. In one molecule, the benzene ring and an attached methoxy group were refined as disordered over two sets of sites in a 0.612(5):0.388(5) ratio. In the same molecule, methanol group is also disordered over two sets of sites in a 0.615(11):0.385(11) ratio. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data collected at room temperature and refined by full-matrix least-squares procedures to a final R-value of 0.0526 for 4066 observed reflections.

X-ray intensity data of 46265 reflections (of which 45604 unique) were collected on *X'calibur* CCD area-detector diffractometer equipped with graphite monochromated MoK α radiation (λ = 0.71073 Å). The crystal used for data collection was of dimensions 0.30 x 0.20 x 0.20 mm. The

cell dimensions were determined by least-squares fit of angular settings of 19712 reflections in the θ range 3.43 to 29.14 ^{o}**.** The intensities were measured by ω scan mode for θ ranges 3.44 to 25.00^{o}. 4066 reflections were treated as observed (I > 2σ (I)). Data were corrected for Lorentz, polarization and absorption factors. The structure was solved by direct methods using SHELXS97. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97. The final refinement cycles converged to an R = 0.0526 and wR (F^2) = 0.1239 for the observed data. Residual electron densities ranged from - 0.222 to 0.190 e$Å^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in Table 1. CCDC - 930264 contains the supplementary crystallographic data for this paper.

Table 2.3 Crystal data and other experimental details of **26t**

CCDC No	930264
Empirical formula	C_{18} H_{22} N_2 O_2
Formula weight	298.38
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, P21
Unit cell dimensions :	a= 9.1775(2), b= 10.7628(2), c=
16.9499(5)Å,	
	β = 107.577(2) ^{o}
Volume	1596.07(7) A Å ^{3}
Z, Calculated density	4, 1.242 Mg/m ^{3}
Absorption coefficient	0.081 mm^{-1}
F(000)	640
Crystal size	0.30 x 0.20 x 0.20 mm
Theta range for data collection	3.44 to 25.00 ^{o}
Limiting indices	-10≤h≤10, -12≤k≤12, -20≤l≤20
Reflections collected / unique	46265 / 5604 [R(int) = 0.0621]
Completeness to theta = 25	00 99.7 %

Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.00000 and 0.90642
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5604 / 269 / 453
Goodness-of-fit on F^2	1.035
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1239
R indices (all data)	R1 = 0.0799, wR2 = 0.1359
Measurement	*X'calibur system – Oxford diffraction make, U.K.*

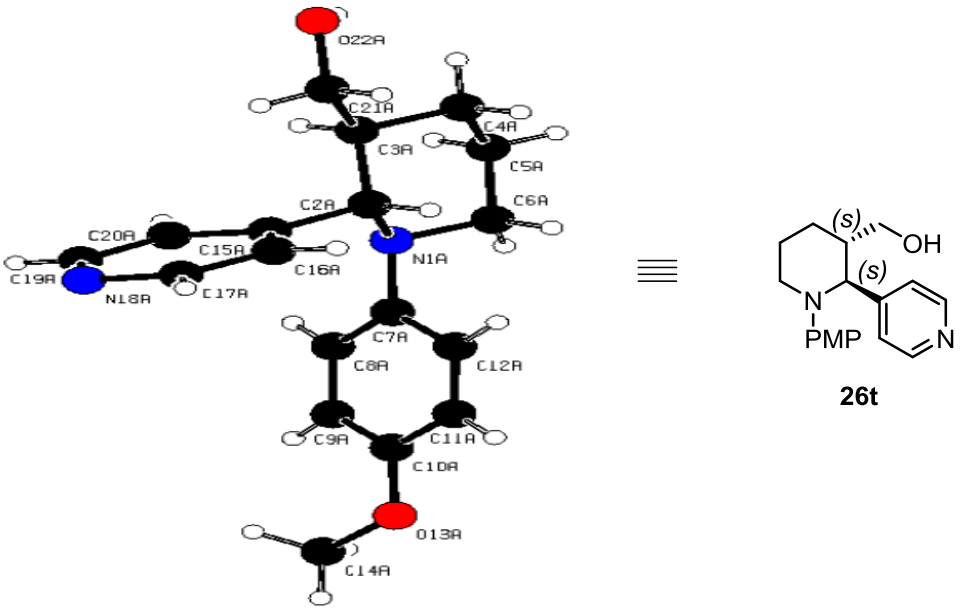


Figure 2.6 X-ray crystal of compound **26t**

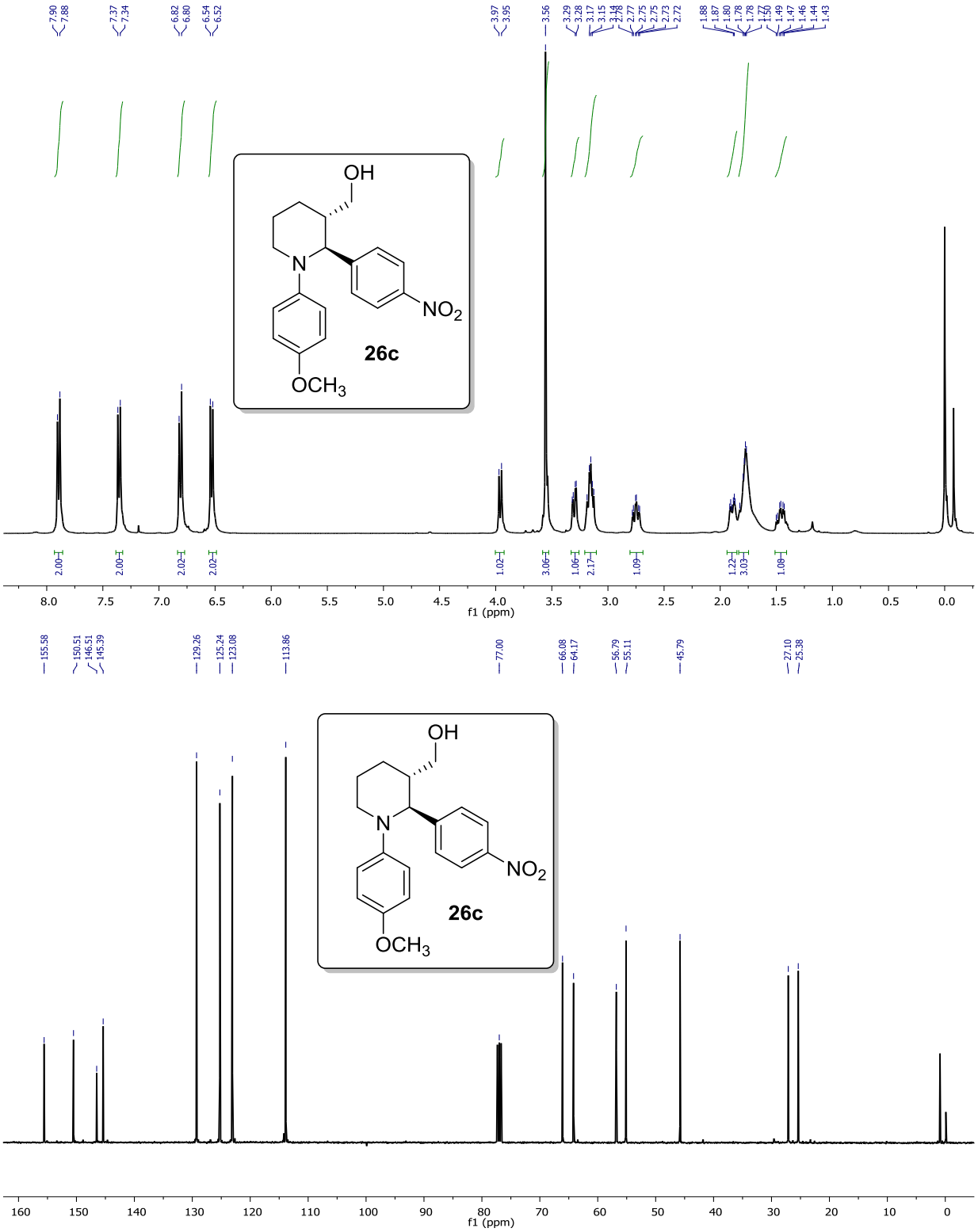
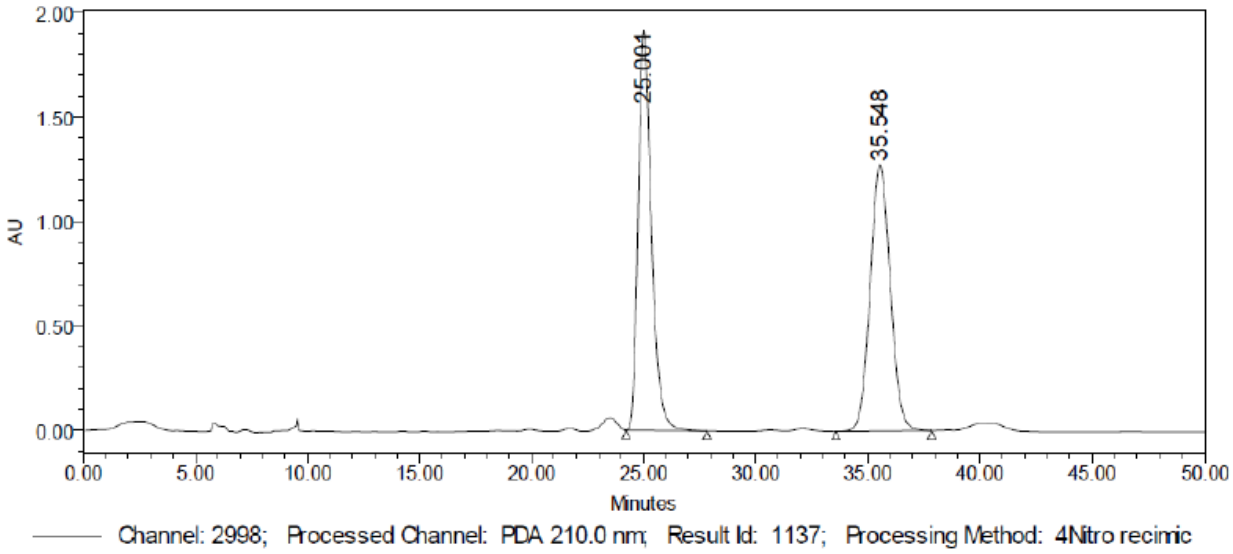
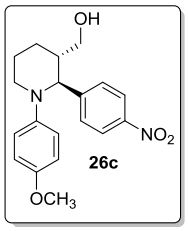


Figure 2.7 ^{1}H and ^{13}C NMR spectra of **26c**

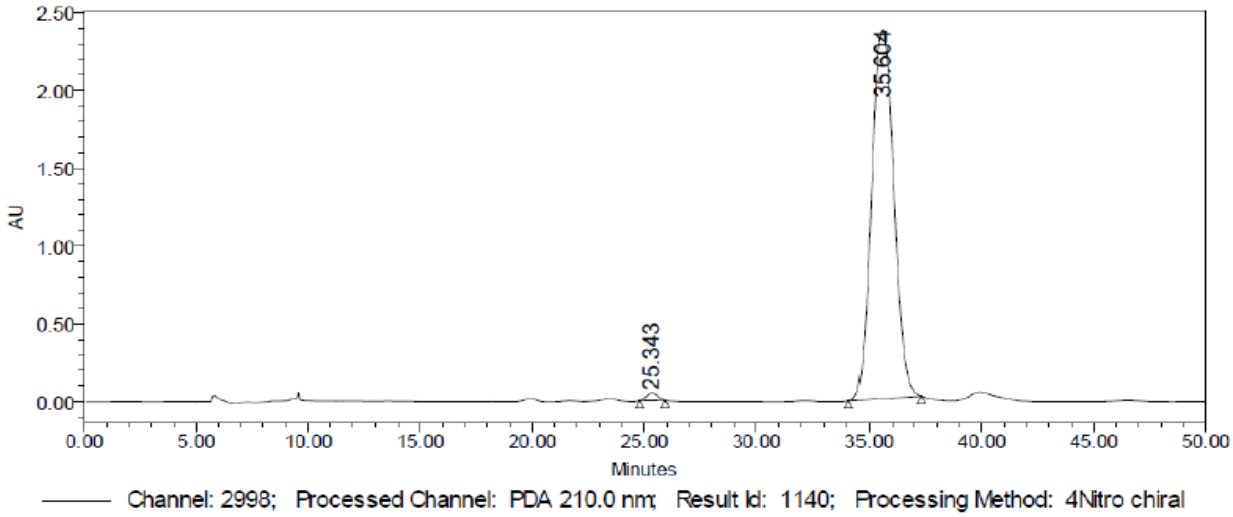


Processed Channel Descr.: PDA 210.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 210.0 nm	25.001	78936708	49.78	1912322
2	PDA 210.0 nm	35.548	79635847	50.22	1274748



26c



Processed Channel Descr.: PDA 210.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 210.0 nm	25.343	1544346	0.94	44023
2	PDA 210.0 nm	35.604	162803331	99.06	2370119

Figure 2.8 HPLC chromatogram of **26c**

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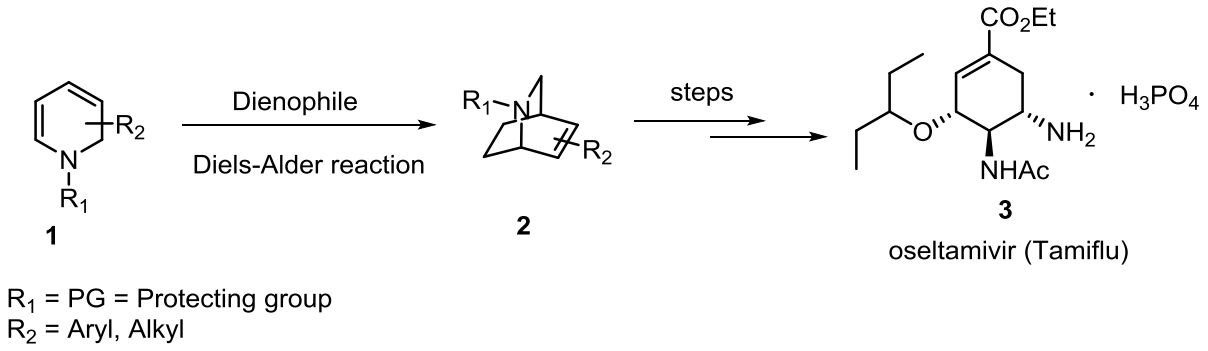
Chapter - 3

Proline Catalyzed Asymmetric synthesis of N-PMP 1,2-dihydropyridines

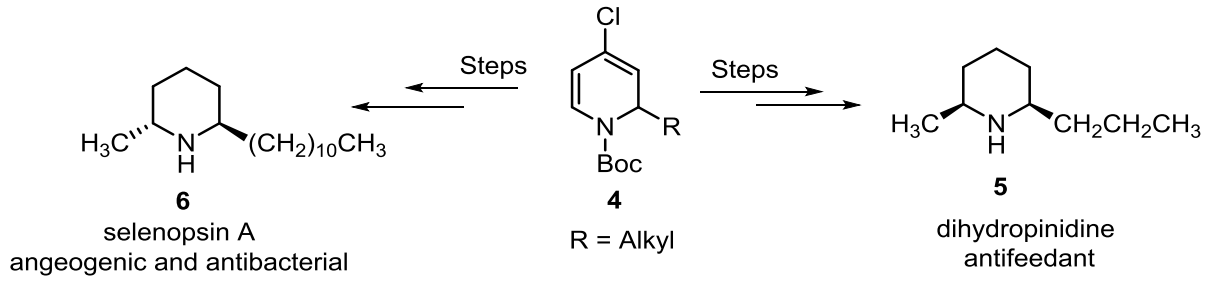
3.1 Introduction

Dihydropyridine is a pyridine based scaffold, which belongs to the class of compounds that have been semi-saturated with two substituents replacing one double bond. They are particularly well known in pharmacology as L-type calcium channel blockers, used in the treatment of hypertension. Compared with certain other L-type calcium channel blockers (for example those of the phenylalkylamine class such as verapamil) which have significant action at the heart, they are relatively vascular selective in their mechanism of action in lowering blood pressure. For many years there has been major interest in the synthesis, synthetic utility, and biological activity of various dihydropyridines. Dihydropyridines (DHPs) are frequently encountered in natural and synthetic compounds that possess many remarkable biological activities.[1-3] In particular, 1,2-dihydropyridines (1,2-DHPs) are important building blocks to synthesize a wide range of organic molecules, as well as functionalized bio active compounds such as piperidine,[4-8] indolizidine,[9-13] quinolizidine,[14-17] and cis-decahydroquinoline [18-20] alkaloids (**Figure 3.1**). This structural unit has also been considered as a suitable substrate to prepare isoquinuclidines **2** and related pharmaceutical drugs **3**,[21-25] through Diels-Alder reaction, and an important structural motif for a variety of complex natural products [26-32] mainly the iboga type indole alkaloids.[33-35] Few important alkaloids and natural products accessed through 1,2-DHPs is shown in **Figure 3.1**.



Scheme 3.1 Synthesis of pharmaceutical drug from 1,2-dihydropyridines [24]

The use of 1,2-DHPs is widely explored for the synthesis of various natural products and alkaloids. Few examples have been discussed in **scheme 3.2**. Comin's group utilized the substituted 1,2-DHPs **4** for the synthesis of dihydropinidine **5** which is antifeedant as well as for the synthesis of selenopsin A **6** alkaloid which is a useful antibacterial agent.



Scheme 3.2 Synthesis of alkaloids from 1,2-dihydropyridines[8]

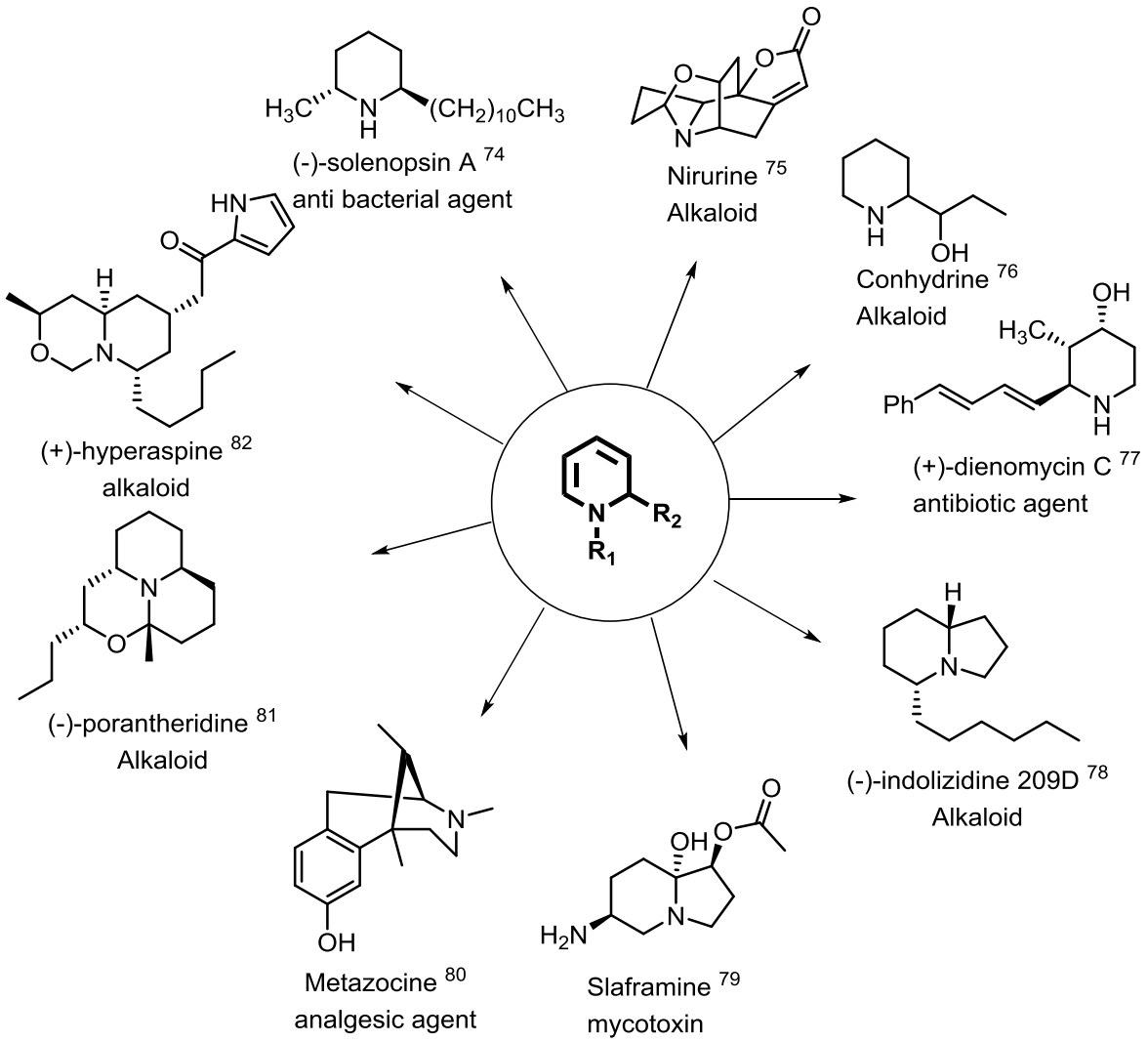
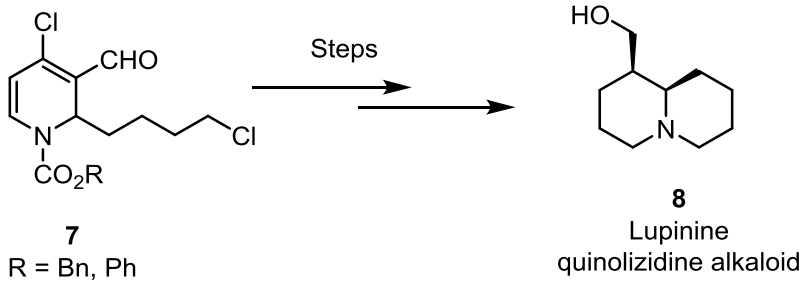


Figure 3.1 Few alkaloids and drug molecules originated from 1,2-DHPs

The 2,3,4-substituted 1,2-DHPs 7 with appropriately substituted leaving group at the terminal of the hydrocarbon chain for cyclization, was utilized for the synthesis of biologically important quinolizidine alkaloid **8** by Comin's group as shown in the **Scheme 3.3**.



Scheme 3.3 Synthesis of quinolizidines from 1,2-dihydropyridines [36]

Owing to the high synthetic and biological importance of 1,2-DHPs, a number of methods have been established for their synthesis.[37,38] More strictly, these synthetic efforts can be broadly divided into two main categories: *(i) Nucleophilic addition to activated pyridines* (Path 1, **Figure 3.2**),[39-43] *(ii) 6π-electrocyclization of 1-azatrienes* (Path 2, **Figure 3.2**).[44-52]

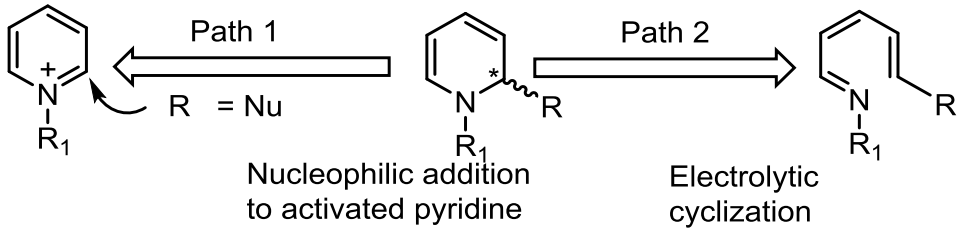
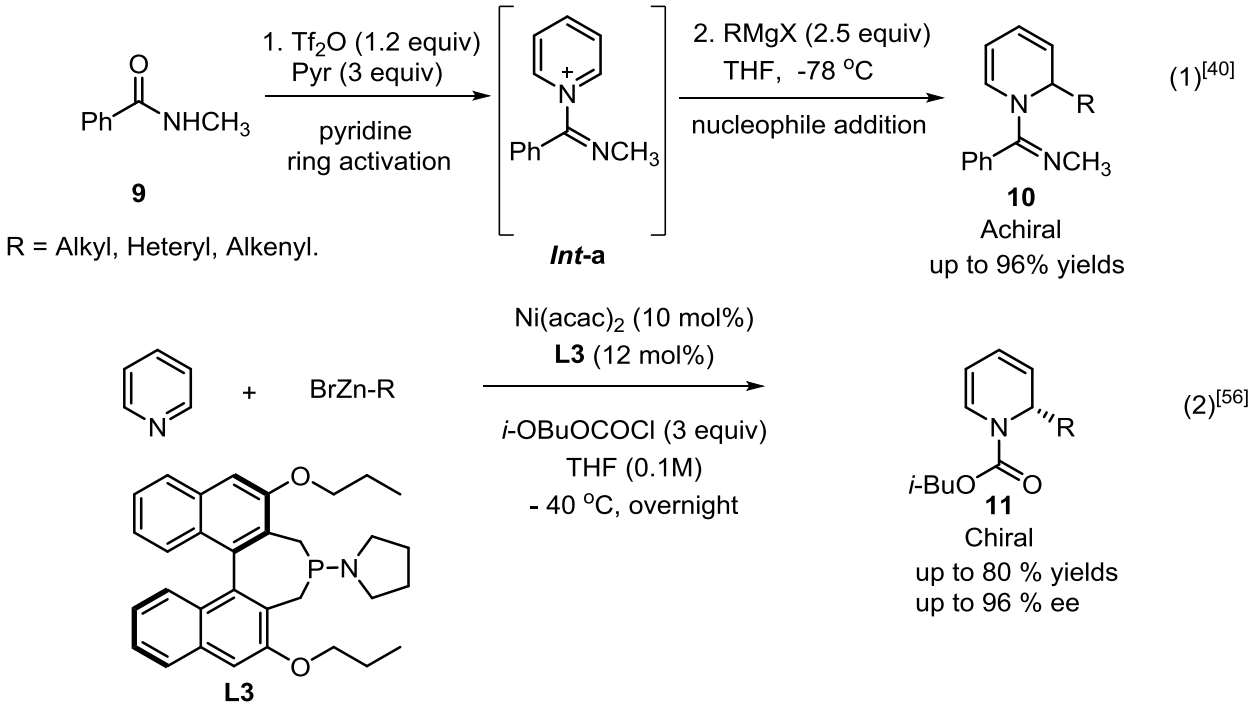


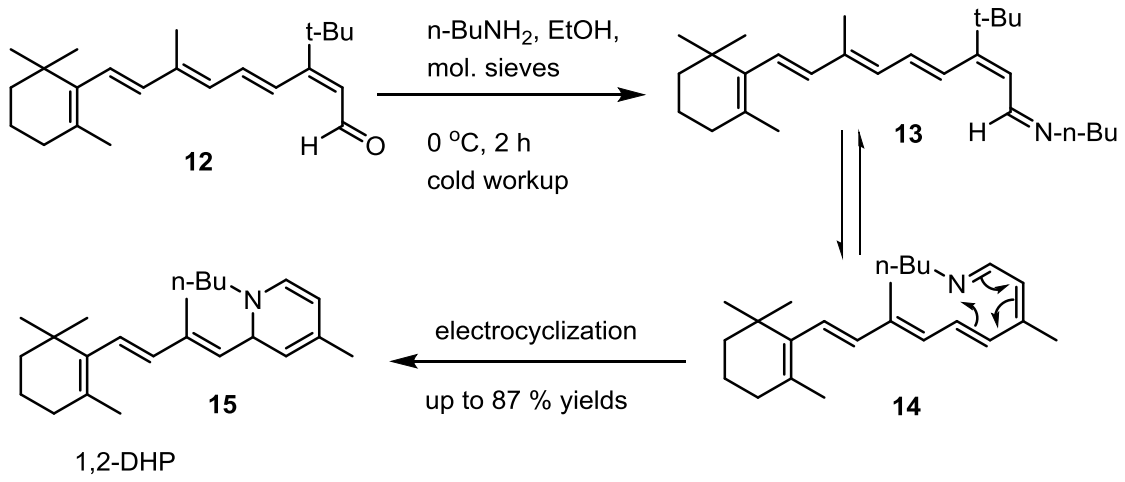
Figure 3.2 General synthetic approaches for 1,2-dihydropyridines (DHPs)

***(i) Nucleophilic addition to the activated pyridine*:** Pyridine molecule was activated with an electron withdrawing functional group **9** followed by nucleophilic addition at C2 position of the in situ generated electron deficient pyridine ring ***Int*-a** produced 1,2-DHPs **10** in achiral fashion was reported by Comin's group.[40] Few graceful asymmetric synthetic methods for the synthesis of chiral 1,2-DHPs were reported,[53-56] although they possess experimental limitations like tedious pre-activation. Latest one of them is shown in (eq. 2, **Scheme 3.4**), where the chiral ligand was used in the reaction to make the reaction enantioselective to produce the chiral 1,2-DHP **11** in good yields and enantioselectivities.



Scheme 3.4 Activation of pyridine for 1,2-DHPs synthesis

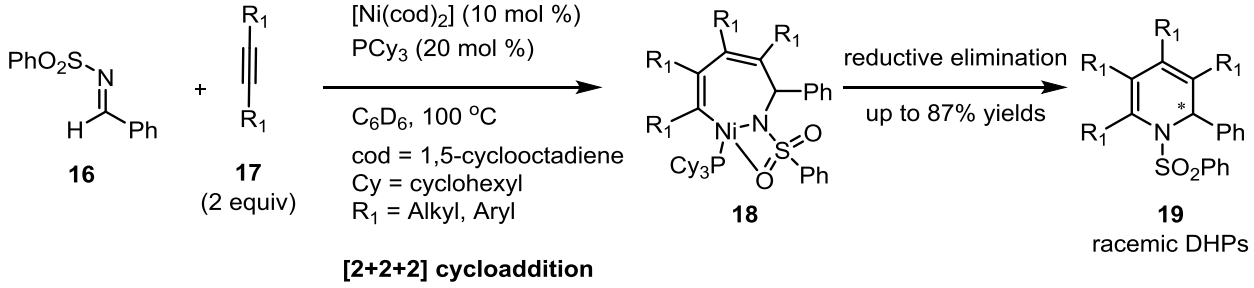
(ii) 6π-electrocyclization of 1-azatrienes: Maynard and Okamura reported the in situ generated aza trienes **14** derived from enals **12** and amines underwent 6π-electrocyclization for the synthesis of 1,2-DHPs **15.** [44]



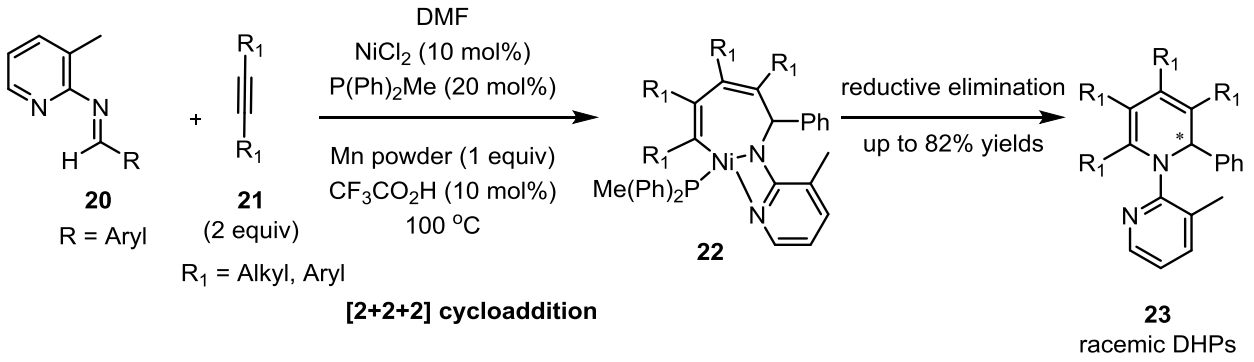
Scheme 3.5 Electrocyclization strategy for the synthesis of 1,2-DHP[44]

Alternatively, methods involving imines as suitable unsaturated partners to synthesize 1,2-DHPs have some success.[57-62] Initially, the Ogoshi group have developed a new method for 1,2-DHPs **19** which preceded through metal catalyzed [2+2+2] cycloaddition reaction between alkynes **17** and *N*-sulfonyl **16,** [57,58] or *N*-aryl imines.[59] Similar cycloaddition was independently explored

by Yoshikai and co-workers using *N*-pyridyl imines **20**.[60] Both of these strategies preceded *via* oxidative insertion of nickel, forming a complex **18,** and **22** (**schemes 3.6, 3.7 respectively**) which underwent reductive elimination of the metal-ligand portion leaving the ring closed in the consecutive step. These approaches were mainly restricted to produce racemic 1,2-DHPs as shown in **scheme 3.6**.

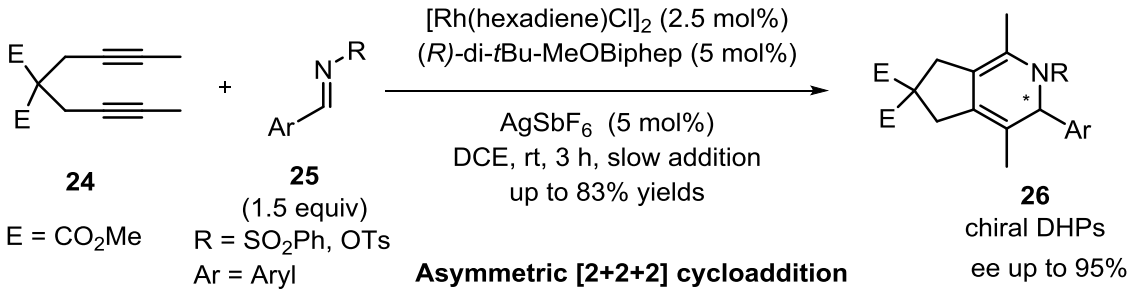


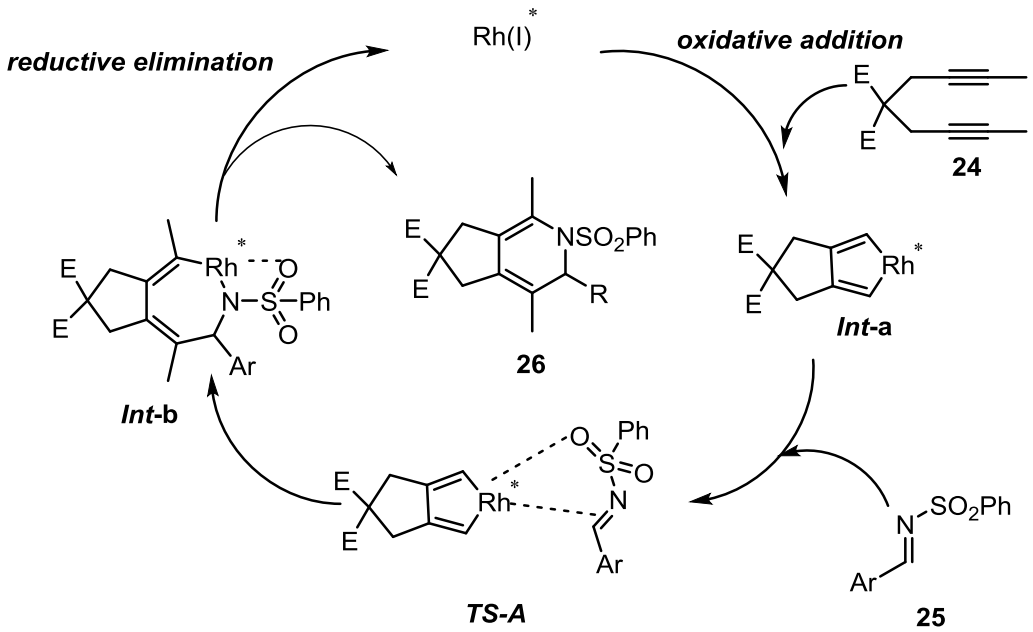
Scheme 3.6 [2+2+2] cycloaddition involving sulfonyl imine for 1,2-DHPs [57]



Scheme 3.7 [2+2+2] cycloaddition involving pyridyl imine for 1,2-DHPs[60]

Recently, V. Gandon and co-workers developed the first asymmetric variant of this metal-catalyzed [2+2+2] cycloaddition between diynes **24** and *N*–sulfonimines **25** as well as with *N*–tosyl imines. (**Scheme 3.8**).[63] The reaction involved a chiral ligand-metal complex mediated oxidative insertion to a diyne **24** produced ***intermediate*-a** followed by *trans-metallation* through transition state (***TS-A***) given the ***intermediate*-b.** This consequent reductive elimination of metal complex from ***intermediate*-b** produced the chiral 1,2-DHPs **26** in good yields and enantio selectivities. The tedious procedure to prepare diyne starting material and chiral ligand is the main drawback of this methodology. On the other hand, heavy metal pollution and the scalability of the reaction are the main dis advantages of this methodology.

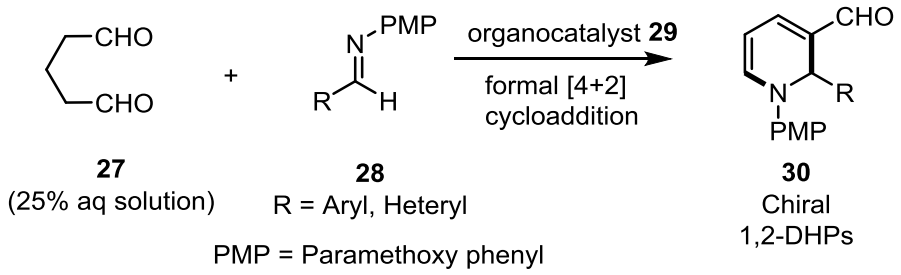




Scheme 3.8 Asymmetric [2+2+2] cycloaddition involving imine for chiral DHPs [63]

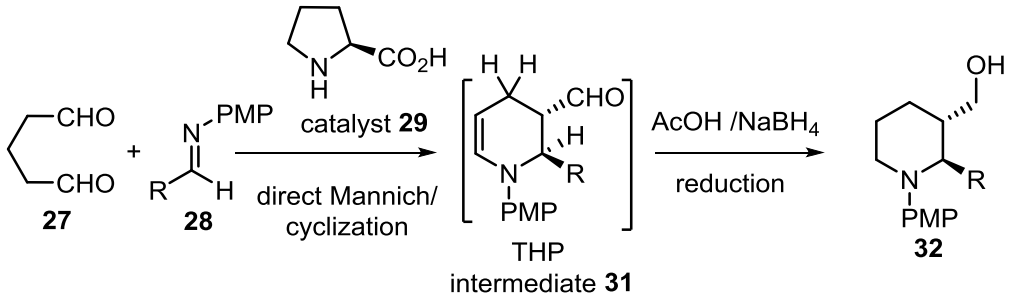
3.2 Results and discussion

Despite of few efforts for asymmetric synthesis of 1,2-DHPs, the development of a simple and efficient enantioselective method to access 1,2-DHPs presents a difficult task and is still in high demand. Hence, we developed a straightforward one-pot strategy for the enantioselective synthesis of *N*-PMP-1,2-DHPs **30** (PMP = *p*-$OMeC_6H_4$) from inexpensive materials with high yields and enantioselectivities under mild reaction conditions through organocatalysis (**Scheme 3.9**).[64]



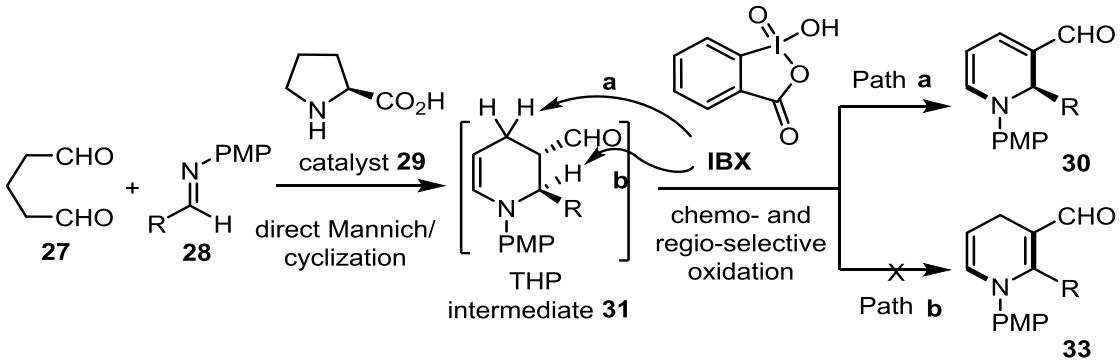
Scheme 3.9 Involvement of PMP imines in [4+2] cycloaddition for chiral 1, 2-DHPs

Recently, we have developed a formal [4+2] cycloaddition reaction between glutaraldehyde and imine through proline catalyzed direct Mannich reductive cyclization reaction producing chiral piperidines **32** in high yields and enantioselectivities, which was discussed in chapter 2.



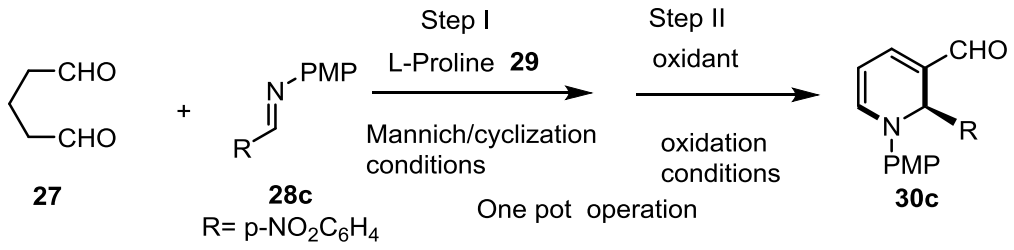
Scheme 3.10 L-Proline catalyzed formal [4+2] cycloaddition for enantioselective synthesis of piperidine

We further envisioned that in situ site-selective oxidation of THPs compound **31** could lead to the synthesis of DHPs (**Scheme 3.11**). Interestingly, the oxidation of the **31** could occur at the two different places, which could subsequently give 1,2-DHPs **30** (Path a, **Scheme 3.11**) or 1,4-DHPs **33** (Path b, **Scheme 3.11**). Keeping this idea in mind, we established a reaction conditions for one-pot asymmetric synthesis of 1,2-DHPs **30** as shown in **Table 3.1**.



Scheme 3.11 IBX mediated chemo- and regio-selective dehydrogenative oxidation of THP **31**

Table 3.1 Optimization of reaction conditions (**30c**)

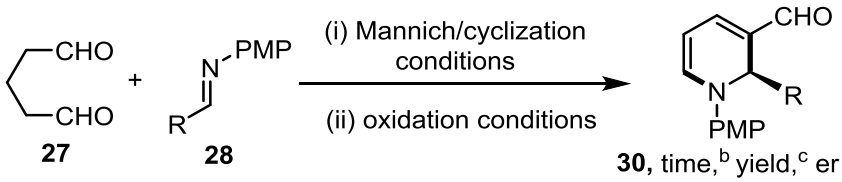


entry	Step I[a]	Step II	yield (%)[b]	er[c]
1	DMSO, rt, 5 h	DDQ, rt, 12 h	-	-
2	DMSO, rt, 5 h	SeO_2, rt, 6 h	-	-
3	DMSO, rt, 5 h	IBX, 70 ^oC, 3 h	76	88:12
4	DMSO, 10 ^oC, 6 h	IBX, 40 ^oC, 4 h	87	93:7
5	DMSO, 10 ^oC, 6 h	IBX, rt, 6 h	76	93:7
6	DMSO, 10 ^oC, 6 h	IBX, 10 ^oC, 9 h	65	93:7
7[d]	DMSO, 10 ^oC, 12 h	IBX, 40 ^oC, 4 h	58	93:7

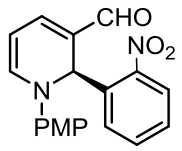
[a] Unless otherwise indicated, the reaction was carried out at (i) **28c** (0.3 mmol), **27** (25% aqueous sol., 0.9 mmol), L-Proline **29** (20 mol %), solvent (3.0 mL) (ii) oxidant (120 mol %). [b] Isolated yield of **30** refer to **28c**. [c] Determined using stationary chiral columns. [d] Catalyst **29** (10 mol %).

Our initial attempts failed to give any DHPs (**30** or **33**) through in situ oxidation of THP intermediate **31** in DMSO when either DDQ, or SeO_2 used (entry 1 and 2, **Table 3.1**). Gratifyingly, *N*-PMP-1,2-DHP **30c** was obtained as sole product with good yield (76%) and enantioselectivity (88:12 er), when IBX (2-Iodoxybenzoic acid) was used as oxidizing agent at 70 ^oC in the same flask (entry 3, **Table 3.1**). This one-pot transformation was made feasible by taking advantage of IBX solubility in DMSO as well as the ability to dehydrogenate carbonyls into corresponding α, β-unsaturated carbonyls.[65] Here, the exclusive production of 1,2-DHPs **30** could be justified through chemo- and regio-selective oxidation of intermediate **31** by using bulky IBX at less substituted allylic position C4 (Path a, **Scheme 3.11**). While, oxidation at more substituted position C2 (Path b, **Scheme 3.11**) was not observed. Enhancement in the yield (87%) and enantioselectivity (93:7 er) was observed when Proline-catalyzed direct Mannich/ cyclization sequence was carried out at 10 ^oC followed by in situ IBX oxidation at 40 ^oC.

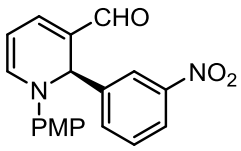
Table 3.2 Substrate scope for 1,2-DHPs (**30**)



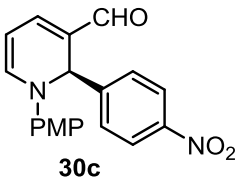
27 **28** **30,** time,[b] yield,[c] er [d]



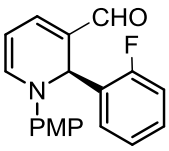
30a
9h, 68%,
99:1 er



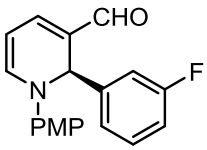
30b
8h, 83%,
98:2 er



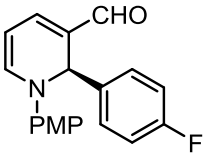
30c
6h, 87%,
97:3 er



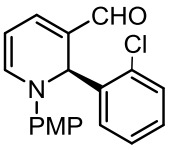
30d
9h, 69%,
96:4 er



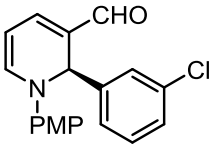
30e
8h, 71%,
93:7 er



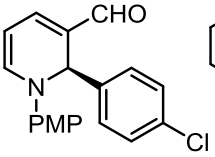
30f
8h, 77%,
88:12 er



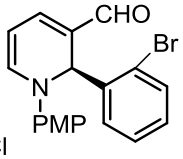
30g
9h, 68%,
96:4 er



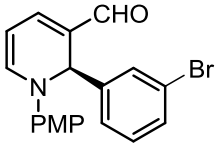
30h
8h, 70%,
95:5 er



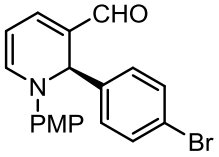
30i
8h, 73%,
90:10 er



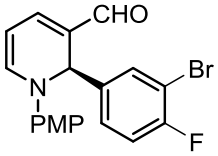
30j
10h, 68%,
98:2 er



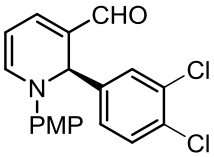
30k
9h, 74%,
93:7 er



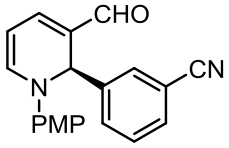
30l
9h, 79%,
91:9 er



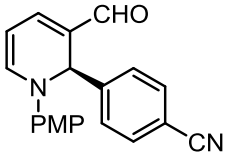
30m
8h, 72%,
95:5 er



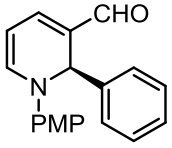
30n
8h, 70%,
97:3 er



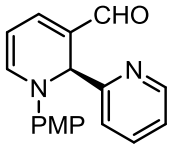
30o
9h, 72%,
84:16 er



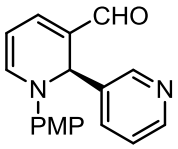
30p
9h, 70%,
94:6 er



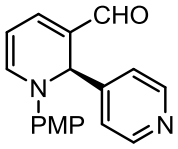
30q
9h, 66%,
88:12 er



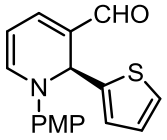
30r
8h, 67%,
94:6 er



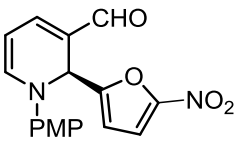
30s
9h, 71%,
84:16 er



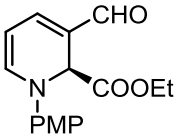
30t
8h, 73%,
92:8 er



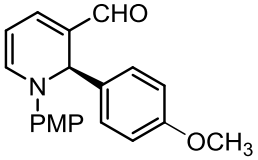
30u
9h, 67%,
88:12 er



30v
8h, 71%,
87:13 er



30w [e]
6h, 87%,
>99:1 er



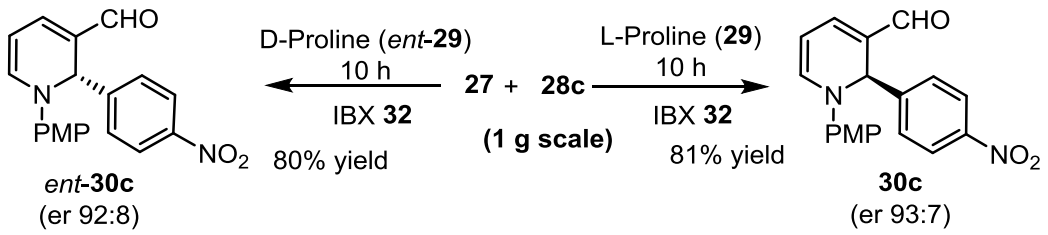
30x
n.r

[a]Unless otherwise indicated, the reaction was carried out at (*i*) **28** (0.3 mmol), **27** (25% aqueous sol., 0.9 mmol), L-Proline **29** (20 mol %), DMSO (3.0 mL) (*ii*) IBX **32** (120 mol %), 40 ^{o}C, 4 h. [b]Time for direct Mannich/cyclization reaction. [c]Isolated yield. [d]Determined using stationary chiral columns. [e]Reaction was carried out without water.

Further decreasing the reaction temperature during IBX oxidation (entry 5 and 6, **Table 3.1**) and catalyst loading (entry 7, **Table 3.1**) led to extended reaction time with reduced yields without variation in enantioselectivity. Thus, we preferred to perform this one-pot two-steps sequence to *N*-PMP-1,2-DHPs **30** with optimized conditions (entry 4, **Table 3.1**).

The scope of this method was then investigated to confirm its robustness with regard to a variety of preformed imines **28** under optimized conditions and the results are summarized in **Table 3.2** The reaction proceeded well with good yields and enantioselectivity in almost all cases when electron withdrawing groups (EWG) (e.g. $-NO_2$, −F, −Cl, −Br and –CN) were substituted at the ortho-, meta- or para-positions on the aryl imines (**30a-30p**, **Table 3.2**). However, the reactions were rather slow in case of aryl imines substituted at ortho, possibly due to steric effect (**30a, 30d, 30g, 30j**, **Table 3.2**). Pleasingly, hetero-aromatic imines also gave the corresponding products (**30r**-**30v**) (**Table 3.2**) in good yields and enantioselectivity under this optimized condition. A clean transformation to highly functionalized *N*-PMP-1,2-DHP **30w** was observed with high yields (90%) and excellent selectivities (>99:1 er), when activated imine **28w** was utilized without water. This reaction has limitation to electron deficient imines as reaction failed to produce 1,2-DHP **30x** in case of electronically rich arylimine **28x**.

Next we decided to prepare *N*-PMP-1,2-DHPs **30** in reasonably good amount and in stable form. The presence of a –CHO group at C3 provides stabilization, as electron-withdrawing substituents stabilizes DHPs. To fulfill the first objective and to demonstrate the practical utility of our protocol, we prepared both enantiomers of 1,2-DHPs at gram scale by utilizing both L- and D-Proline as catalysts. While a somewhat longer reaction time was required, **30c** and *ent*-**30c** were obtained without much reduction in yields and with same selectivity from **28c** (1.0 g) as shown in **Scheme 3.12**. Easy availability of starting materials, glutaraldehyde **27**, imines **28** and metal-free access to both enantiomers of *N*-PMP-1,2-DHPs, makes this approach quite practical and attractive.



Scheme 3.12 Gram scale synthesis of both enantiomers of *N*-PMP-1,2-DHP (**30c** and *ent*-**30c**)

Single crystal X-ray study of **30b** and **30w** further confirmed the stereochemical outcome at C2 (**Figure 3.3**), as expected through L-Proline **29** catalyzed *syn*-Mannich reaction[66-68]/intramolecular cyclization/oxidation sequence. The absolute stereochemistry of all other products was assigned through analogy.

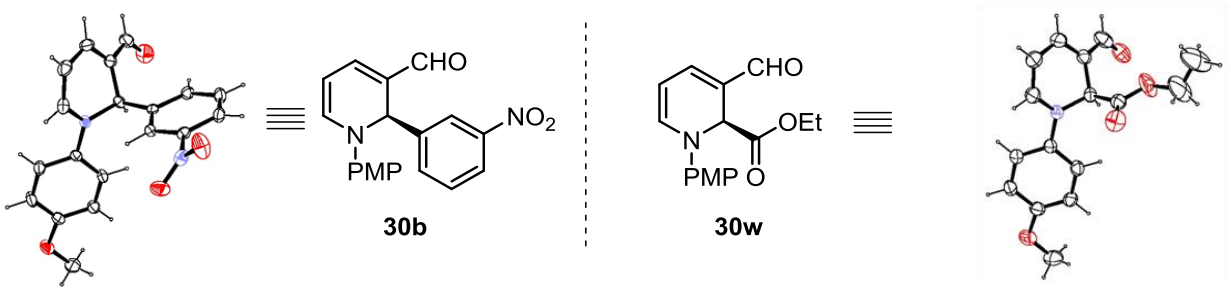
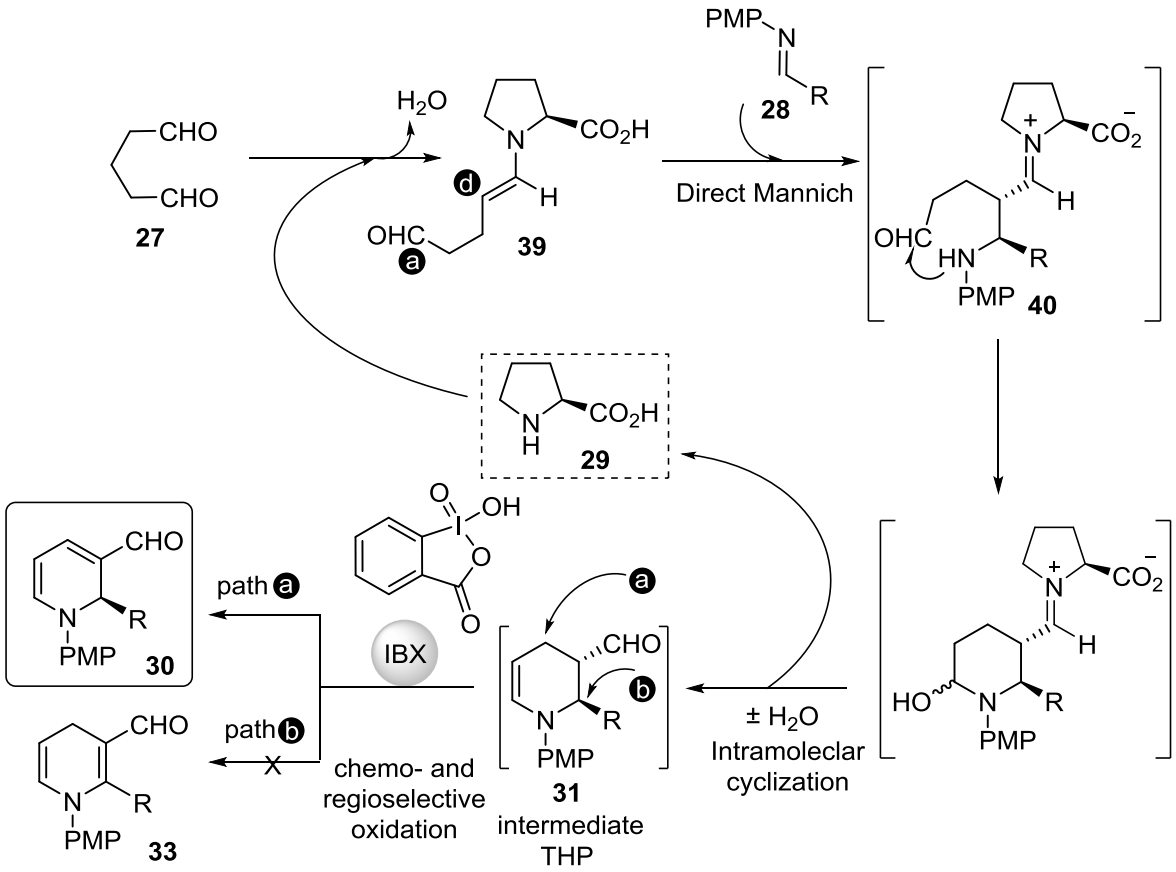


Figure 3.3 Absolute stereochemistry through ORTEP diagrams of **30b** and **30w**

3.3 Plausible Mechanism

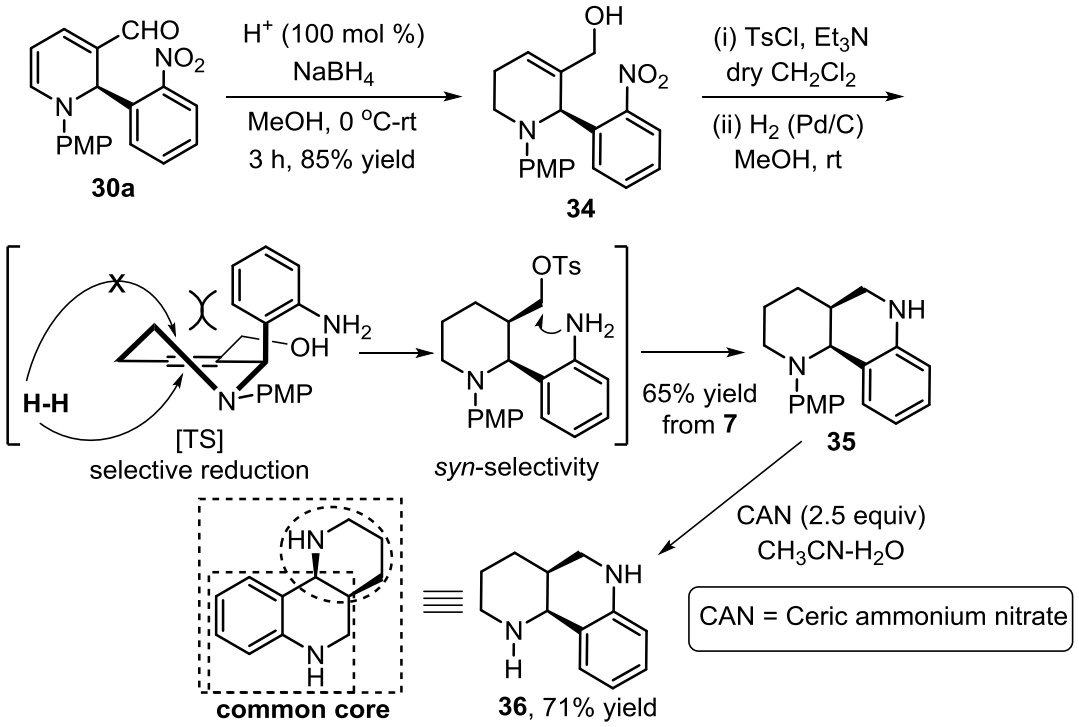
A complete plausible mechanism has been proposed to rationalize the high stereo-chemical outcome of this transformation. Plausible mechanism for the synthesis of enantioselective synthesis of piperidines proceeded through organocatalytic Mannich reaction of glutaraldehyde **27** followed by intramolecular cyclization of **40** and consequent dehydration of the unstable intermediate produced the enamine intermediate **31**. The IBX mediated regeoselective dehydrogenation of enamine intermediate **31** produced the functionalized piperidine 1,2-DHPs in the same pot as shown in the following **Scheme 3.13**



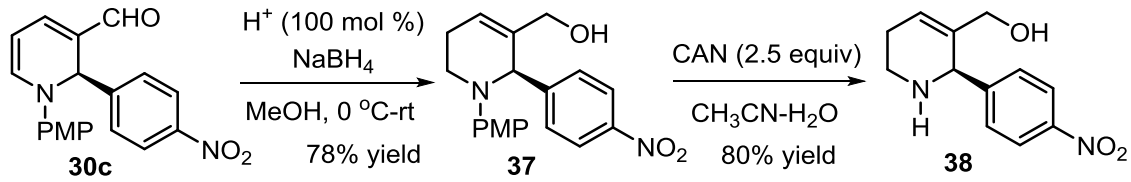
Scheme 3.13 Detailed plausible mechanism for the asymmetric synthesis of 1,2-DHPs **30** from gluteraldehyde **27** and *N*-PMP-imines **28**

In order to show the synthetic application of our strategy, we converted one of our compound **30a** into fused polycyclic compound **35** using the sequence of synthetic transformation as shown in **Scheme 3.14**. Initially, **30a** was reduced to tetrahydropyridine (THP) **34** constituted with allylic alcohol group using acidic $NaBH_4$ in 85% yield. Next, alcohol group was converted into –OTs under standard condition and catalytic hydrogenation using Pd/C and $(H_2)_{(g)}$ was performed with crude material without purification. The reduction of $–NO_2$ and alkene groups takes place under this condition as expected. Interestingly, intramolecular cyclization of in situ generated amine furnished polycyclic alkaloid-type product **35** having *syn*-stereochemistry at two chiral centers in the same pot. Our initial efforts to convert **30a** directly to **35** through one pot reduction of all alkene bonds and $–NO_2$ group, followed by reductive cyclization with aldehyde under different reaction conditions, failed. After PMP removal from **35**, a fused product **36** was obtained, which contains tetrahydroquinoline and piperidines moieties. These units are key elements found in numerous biologically active natural products and synthetic

pharmaceuticals.[69-73] *N*-PMP deprotection from 1,2-DHP **30** was failed, while this deprotection was successfully demonstrated from *N*-PMP-tetrahydropyridine **37** to highly functionalized tetrahydropyridine **38** as shown in **Scheme 3.15**. This compound can be further transformed to various piperidine derivatives.



Scheme 3.14 Application of 1,2-DHPs for the synthesis of alkaloid common core skeleton



Scheme 3.15 Deprotection of PMP group for further functionalization of free N-H

3.4 Conclusions:

In conclusion, we have developed an operationally simple first metal-free enantioselective synthesis of *N*-PMP-1,2-dihydropyridines **30** via one-pot formal [4+2] cycloaddition between readily available aldimines **28** and aqueous glutaraldehyde **27**. This reaction proceeds through Proline **29** catalyzed direct Mannich/cyclization, followed by IBX mediated site-selective dehydrogenative-oxidation sequence with high yields and selectivity. The viability of this method was established through; (*i*) gram scale synthesis of both enantiomers of *N*-PMP-1,2-DHPs **30c**,

(*ii*) quick synthesis of fused chiral tetrahydroquinoline based important alkaloid skeleton **36**. This novel strategy sets the stage for the synthesis of chiral isoquinuclidines and their applications in natural product synthesis.

3.5 General Experimental Information:

Infrared (FT-IR) spectra were recorded on a Perkin-Elmer Spectrometer, ν_{max} in cm^{-1}. ^{1}H, ^{13}C-NMR spectra were recorded in $CDCl_3$ solution and spectral data were reported in ppm relative to tetramethylsilane (TMS) as internal standard. ^{13}C-NMR spectra were recorded on a BRUKER-AV400 (75 MHz) spectrometer with complete proton decoupling. High resolution mass spectra were recorded using quadruple electro spray ionization (ESI) technique. Enantiomeric ratios (er) were determined by HPLC analysis (Water-2998 Instrument) by using stationary phase CHIRALPAK-IA and IB chiral columns and *i*-PrOH/Hexane as solvent system in comparison with authentic racemic materials. Specific rotation was measured through RUDOLPH Polarimeter. Melting points were determined by EZ–Melt, Automated Melting Point Apparatus (SRS Stanford Research System, SIN: 78476).

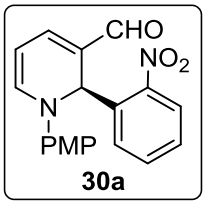
Unless otherwise noted all reactions have been carried out with commercially available analytical grade reagents and freshly distilled solvents without inert atmosphere. All work up and purification were carried out with reagent grade solvents in air. Thin-layer chromatography was performed using Merck silica gel 60 F254 pre-coated plates (0.25 mm). Column chromatography was performed using silica gel (100-200 mesh) using the mixture of Hexane-EtOAc as eluting solvent.

3.6 General procedure for the synthesis of 1,2–dihydropyridines:

Typical procedure for the synthesis of 30: Glutaraldehyde **27** (25% in water, 0.360 mL, 0.9 mmol) was added to a mixture of preformed *N*-PMP imine **28** (0.3 mmol) and L-Proline **29** (6.9 mg, 0.06 mmol) in DMSO (3.0 mL) at 10 ^{o}C. The reaction mixture was further stirred at the same temperature until the imine was consumed as monitored by TLC. IBX (1.2 equiv, 0.36 mmol) was added into the same flask and further heated at 40 ^{o}C for 4 hrs. Reaction was quenched with saturated $NaHCO_3$ (20% sol.). The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine once and dried over anh. Na_2SO_4 and concentrated in vacuo. Purification was performed by a silica gel column and eluted with hexane/EtOAc to give product **30** (62-87% yields). The enantiomeric ratios (er) of the products were determined by stationary chiral phase HPLC analysis.

3.7 Characterization data:

(*R*)-1-(4-methoxyphenyl)-2-(2-nitrophenyl)-1,2-dihydropyridine-3-carbaldehyde (30a):

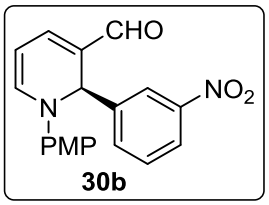


30a

Dark red viscous liquid, (68 mg), 68% yield, $[\alpha]_D^{25}$ = – 52.8 (*c* 0.1, CH_2Cl_2, er 99:1); IR (KBr)/cm^{-1} 2920, 2853, 1631, 1545, 1506, 1348, 1250, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 5.22 (t, *J* = 6.6 Hz, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 6.6 Hz, 1H), 7.08 (s, 1H), 7.10–7.14 (m, 3H), 7.70–7.74 (m, 2H) 8.10 (d, *J* = 7.9 Hz, 2H), 9.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.52, 60.38, 96.21, 114.49 (2C), 122.75 (2C), 124.26, 124.96, 128.82, 128.89, 130.09, 133.24, 136.62, 137.89, 142.08, 142.84, 157.46, 188.08; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}N_2O_4$]: 337.1188, found: 337.1190.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IB column (*n*-Hexane: *i*-PrOH = 92:08), 0.5 mL/min; minor enantiomer t_R = 25.980 min, major enantiomer t_R = 27.705 min.

(*R*)-1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1,2-dihydropyridine-3-carbaldehyde (30b):

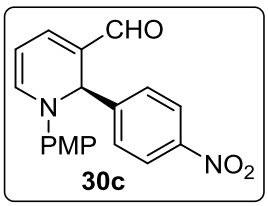


30b

Slight orange color solid, (83 mg), 83% yield, (Melting point = 137-141 ^oC); $[\alpha]_D^{25}$ = – 49.4 (*c* = 0.1, CH_2Cl_2, er = 98:2); IR (KBr)/cm^{-1} 2924, 2852, 1647, 1517, 1508, 1357, 1249, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.48 (t, *J* = 6.6 Hz, 1H), 6.32 (s, 1H), 6.85 (d, *J* = 9.1 Hz, 2H), 6.95–7.00 (m, , 4H), 7.48 (t, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 8.11–8.13 (m, 1H), 8.20 (t, *J* = 1.9 Hz, 1H), 9.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.55, 58.01, 100.08, 114.72 (2C), 120.39, 120.89 (2C), 122.79, 129.77, 132.04, 137.99, 140.00, 141.74, 143.75, 148.39, 152.08, 157.35, 188.95; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}N_2O_4$]: 337.1188, found: 337.1188.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 80:20), 1 mL/min; minor enantiomer t_R = 7.410 min, major enantiomer t_R = 9.908 min.

(*R*)-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1,2-dihydropyridine-3-carbaldehyde (30c):



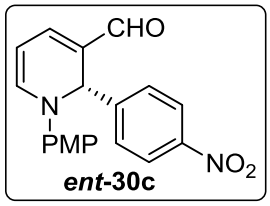
30c

Yellowish oily solid, (87 mg), 87% yield, $[\alpha]_D^{25}$ = – 40.7 (*c* 0.1, CH_2Cl_2, er = 93:7); IR (KBr)/cm^{-1} 2918, 2848, 1629, 1527, 1504, 1348, 1249, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.46 (t, *J* = 6.6 Hz, 1H), 6.32 (s, 1H), 6.85 (d, *J* = 9.1 Hz, 2H), 6.94–6.98 (m, 3H), 7.24 (d, *J* = 6.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 2H), 9.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.52, 58.25, 99.94, 114.72 (2C), 120.82 (2C), 122.65, 123.89 (2C), 126.48

(2C), 137.95, 139.97, 141.78, 147.44, 148.63, 157.37, 188.83; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}N_2O_4$]: 337.1188, found: 337.1191.

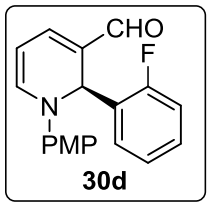
Enantiomeric ratio was determined by HPLC with a Chiralpak-IB column (*n*-Hexane: *i*-PrOH = 88:12), 0.5 mL/min; minor enantiomer t_R = 41.204 min, major enantiomer t_R = 47.118 min.

(*S*)-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1,2-dihydropyridine-3-carbaldehyde (*ent*-30c):



Yellowish oily solid, (1.05 g), 80% yield, ($[\alpha]_D^{25}$ = +38.8 (*c* 0.1, CH_2Cl_2, er = 92.5:7.5); Enantiomeric ratio was determined by HPLC with a Chiralpak-IB column (*n*-Hexane: *i*-PrOH = 88:12), 0.5 mL/min; major enantiomer t_R = 40.398 min, minor enantiomer t_R = 47.656 min.

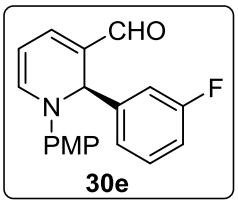
(*S*)-2-(2-fluorophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30d):



Reddish oil, (64 mg), 69% yield, $[\alpha]_D^{25}$ = – 39.4 (*c* 0.3, CH_2Cl_2, 96:4 er); IR(KBr)/cm^{-1} 2916, 2848,1683, 1508, 1246, 1178; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 5.32 (t, *J* = 6.7 Hz, 1H), 6.46 (s, 1H), 6.82 (d, *J* = 9.0 Hz, 2H), 7.02 (m, 3H), 7.05–7.08 (m, 2H), 7.23–7.25 (m, 2H) 7.77 (m, 1H), 9.36 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.32, 57.34, 95.86, 114.28 (2C), 123.77 (2C), 124.33, 127.47, 129.29, 129.38, 129.56, 129.67, 138.24, 140.28, 142.77, 142.97, 157.47, 188.31; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}FNO_2$]: 310.1243, found: 310.1243.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IB column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 16.409 min, major enantiomer t_R = 17.787 min.

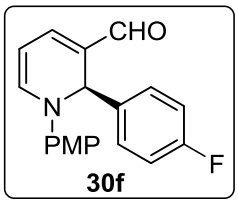
(*R*)-2-(3-fluorophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30e):



Orange viscous liquid, (66 mg), 71% yield, $[\alpha]_D^{25}$ = –36.4 (*c* 0.1, CH_2Cl_2, 93:7 er); IR (KBr)/cm^{-1} 2924, 2848, 1683, 1589, 1247, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.43 (t, *J* = 6.6 Hz, 1H), 6.21 (s, 1H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 6.2 Hz, 1H), 6.94–6.96 (m, 1H), 7.00 (d, *J* = 9.1 Hz, 2H), 7.09–7.12 (m, 1H), 7.19 (m, 2H), 7.23-7.25 (m, 1H), 9.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.50, 58.07, 99.81, 112.46, 112.68, 114.40, 114.54 (2C), 120.72, (2C), 121.07, 123.23, 130.07, 130.16, 138.27, 139.83, 141.52, 157.08, 189.01; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}FNO_2$]: 310.1243, found: 310.1249.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 92:08), 0.5 mL/min; minor enantiomer t_R = 18.690 min, major enantiomer t_R = 25.223 min

(*R*)-2-(4-fluorophenyl)-1-(4-methoxyphenyl)-1, 2-dihydropyridine-3-carbaldehyde (30f):

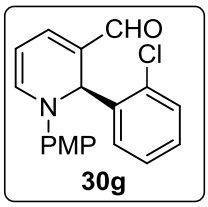


30f

Yellowish pasty liquid, (71 mg), 77% yield, $[\alpha]_D^{25}$ = – 30.6 (*c* 0.1, CH_2Cl_2, 88:12 er); IR (KBr)/cm^{-1} 2927, 2850,1683, 1506, 1456, 1247, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.41 (t, *J* = 6.6 Hz, 1H), 6.18 (s, 1H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.91 (d, *J* = 6.4 Hz , 1H), 6.95 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 9.1 Hz, 2H), 7.16–7.18 (m, 1H), 7.37 (dd, *J* = 8.8 Hz, 5.3 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.53, 58.08, 99.53, 114.57 (2C), 115.27, 115.48, 120.96 (2C), 127.20, 127.28 (2C), 127.73, 130.22, 131.07, 140.04 (2C), 140.37, 141.51, 157.14, 189.11; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}FNO_2$]: 310.1243, found: 310.1245.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 92:08), 0.5 mL/min; minor enantiomer t_R = 13.601 min, major enantiomer t_R = 16.160 min.

(*S*)-2-(2-chlorophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30g):

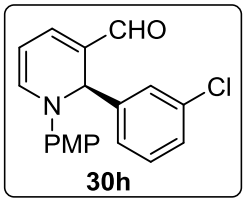


30g

Dark red viscous liquid, (66 mg), 68% yield, $[\alpha]_D^{25}$ = – 58.5 (*c* 0.2, CH_2Cl_2, 96:4 er); IR (KBr)/cm^{-1} 2924, 2850, 1683, 1508, 1436, 1361, 1246 1180; ^1H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 5.20 (t, *J* = 6.6 Hz, 1H), 6.60 (s, 1H), 6.79 (d, *J* = 9.0 Hz, 2H), 6.90 (d, *J* = 6.8 Hz, 1H), 6.99 (d, *J* = 9.1 Hz, 2H), 7.03 (d, *J* = 6.4 Hz, 1H), 7.13–7.17 (m, 2H), 7.18–7.20 (m, 2H), 9.27 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.42, 57.42, 95.92, 114.36 (2C), 123.88 (2C), 124.54, 126.67, 127.54, 128.46, 128.58, 129.37, 129.51, 129.75, 142.65, 142.93, 157.57, 188.34; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}ClNO_2$]: 326.0948, found: 326.0951.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IB column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 18.629 min, major enantiomer t_R = 20.268 min.

(*R*)-2-(3-chlorophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30h):

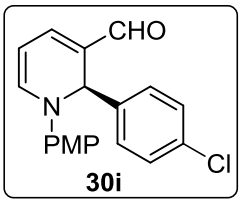


30h

Reddish orange oily solid, (68 mg), 70% yield, $[\alpha]_D^{25}$ = – 52.4 (*c* 0.1, CH_2Cl_2, 95:5 er); IR (KBr)/cm^{-1} 2924, 2848, 1683, 1506, 1456, 1247, 1176; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.44 (t, *J* = 6.7 Hz, 1H), 6.20 (s, 1H), 6.85 (d, *J* = 9.1 Hz, 2H), 6.92 (d, *J* = 6.2 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.20 (m, 1H), 7.22–7.23 (m, 2H), 7.27–7.29 (m, 1H), 7.38 (s, 1H), 9.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.53, 58.05, 99.94, 114.57 (2C), 120.80 (2C), 123.11, 123.72, 125.55, 127.85, 129.94, 134.39, 138.25, 139.85, 141.55, 143.80, 157.12, 189.06; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}ClNO_2$]: 326.0948, found: 326.0948.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 92:08), 0.5 mL/min; minor enantiomer t_R = 16.751 min, major enantiomer t_R = 18.998 min.

(*R*)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30i):

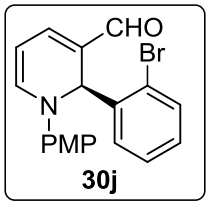


30i

Orange viscous liquid, (71 mg), 73% yield, $[\alpha]_D^{25}$ = – 45.7 (*c* 0.1, CH_2Cl_2, 90:10 er); IR (KBr)/cm^{-1} 2954, 2850,1683, 1506, 1456, 1247, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.41 (t, *J* = 6.6 Hz, 1H), 6.18 (s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 6.2 Hz , 1H), 6.99 (d, *J* = 9.1 Hz, 2H), 7.18 (d, *J* = 6.8 Hz, 1H), 7.25 (m, 1H), 7.33 (d, *J* = 8.5 Hz, 2H), 7.41–7.43 (m, 1H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.53, 58.01, 99.69, 114.55 (2C), 120.84 (2C), 123.41, 126.95 (2C), 128.71 (2C), 133.40, 138.28, 139.92, 140.33, 141.52, 157.12, 189.07; HRMS (ESI): $[MH^+]$ calcd for $[C_{19}H_{16}ClNO_2]$: 326.0948, found : 326.0944.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 80:20), 1 mL/min; minor enantiomer t_R = 8.844 min, major enantiomer t_R = 10.246 min.

(*S*)-2-(2-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30j):

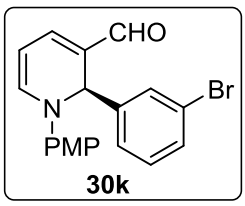


30j

Reddish pasty liquid, (75 mg), 68% yield, $[\alpha]_D^{25}$ = – 67.0 (*c* 0.2, CH_2Cl_2, 98:2 er); IR (KBr)/cm^{-1} 2924, 2848,1676, 1506, 1458, 1247, 1174; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.39 (t, *J* = 6.6 Hz, 1H), 6.17 (s, 1H), 6.60–6.64 (m, 1H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 6.2 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 2H), 7.18 (d, *J* = 6.4 Hz, 1H), 7.28 (s, 1H), 7.41 (d, *J* = 8.4 Hz, 2H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.41, 60.07, 95.45, 114.32 (2C), 124.63 (2C), 124.96, 127.25, 128.29, 128.82, 128.95, 129.62, 129.92, 132.81, 138.31, 138.99, 157.73, 188.35; HRMS (ESI): $[MH^+]$ calcd for $[C_{19}H_{16}BrNO_2]$: 370.0442, found: 370.0448.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IB column (*n*-Hexane: *i*-PrOH = 98:02), 0.5 mL/min; minor enantiomer t_R = 17.156 min, major enantiomer t_R = 19.946 min.

(*R*)-2-(3-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30k):



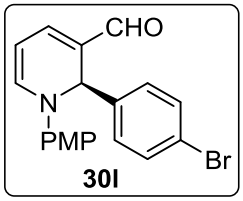
30k

Orange viscous liquid, (82 mg), 74% yield, $[\alpha]_D^{25}$ = –59.8 (*c* 0.1, CH_2Cl_2, 93:7 er); IR (KBr)/cm^{-1} 2922, 2850,1683, 1508, 1456, 1247, 1176; ^1H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.44 (t, *J* = 6.6 Hz, 1H), 6.19 (s, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.92 (d, *J* = 6.2 Hz, 1H), 7.00 (d, *J* = 9.0 Hz, 2H), 7.14–7.26 (m, 3H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.53 (s, 1H), 9.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.52, 58.00, 99.93, 114.56 (2C), 120.79 (2C), 122.62, 123.07, 124.19, 128.38,

130.21, 130.78, 138.22, 139.82, 141.52, 144.00, 157.11, 189.00; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}BrNO_2$]: 370.0442, found: 370.0445.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 92:08), 0.5 mL/min; minor enantiomer t_R = 17.537 min, major enantiomer t_R = 20.900 min.

(*R*)-2-(4-bromophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30l):

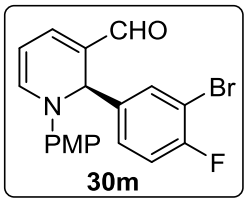


30l

Light yellow oily solid, (87 mg), 79% yield, $[\alpha]_D^{25}$ = – 51.6 (*c* 0.1, CH_2Cl_2, 91:9 er); IR (KBr)/cm^{-1} 2926, 2850, 1683, 1508, 1244, 1180; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.42 (t, *J* = 6.6 Hz, 1H), 6.17 (s, 1H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.91 (d, *J* = 6.2 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 2H), 7.19 (d, *J* = 6.8 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 9.37 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.51, 58.02, 99.71, 114.53 (2C), 120.80(2C), 121.54, 123.23, 127.77 (2C), 131.63 (2C), 138.22, 139.95, 140.80, 141.60, 157.10, 189.07; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{16}BrNO_2$]: 370.0442, found: 370.0442.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 92:08), 0.5 mL/min; minor enantiomer t_R = 30.108 min, major enantiomer t_R = 36.392 min.

(*R*)-2-(3-bromo-4-fluorophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30m):

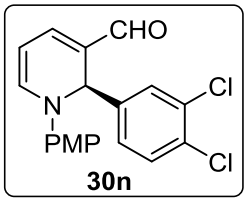


30m

Orange oily solid, (83 mg), 72% yield, $[\alpha]_D^{25}$ = – 48.0 (*c* 0.1, CH_2Cl_2, 95:5 er); IR (KBr)/cm^{-1} 2924, 2852, 1647, 1508, 1249, 1174; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.43 (t, *J* = 6.7 Hz, 1H), 6.17 (s, 1H), 6.85 (d, *J* = 9.1 Hz, 2H), 6.93 (d, *J* = 6.2 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 2H), 7.03 (t, *J* = 8.4 Hz, 1H), 7.18 (d, *J* = 6.2 Hz, 1H), 7.30-7.33 (m, 1H), 7.58 (m, 1H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.43, 57.61, 99.84, 114.54 (2C), 120.70 (2C), 122.78, 125.00, 127.37, 130.51, 131.52, 132.47, 137.96, 139.77, 141.50, 141.91, 157.13, 188.83; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{15}BrFNO_2$]: 388.0348, found: 388.0353.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 80:20), 0.5 mL/min; minor enantiomer t_R = 21.671 min, major enantiomer t_R = 22.703 min.

(*R*)-2-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-1,2-dihydropyridine-3-carbaldehyde (30n):

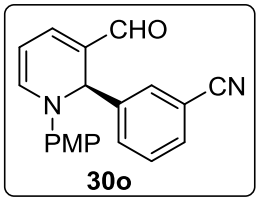


30n

Orange pasty liquid, (75 mg), 70% yield, $[\alpha]_D^{25}$ = – 37.5 (*c* 0.1, CH_2Cl_2, 97:3 er); IR (KBr)/cm^{-1} 2933, 2835, 2358, 1647, 1506, 1247, 1174; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.44 (t, *J* = 6.7 Hz, 1H), 6.17 (s, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 6.3 Hz, 1H), 6.98 (d, *J* = 9.1 Hz, 2H), 7.19 (d, *J* = 6.7 Hz, 1H), 7.25 (dd, *J* = 8.3 Hz, *J* = 2.1 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.49, 57.63, 99.92, 114.57 (2C), 120.76 (2C), 122.75, 125.02, 127.39, 130.56, 131.57, 132.51, 137.99, 139.86, 141.65, 141.90, 157.18, 188.97; HRMS (ESI): $[MH^+]$ calcd for $[C_{19}H_{15}Cl_2NO_2]$: 360.0558, found: 360.0564.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 86:14), 0.5 mL/min; minor enantiomer t_R = 18.357 min, major enantiomer t_R = 19.211 min.

(*R*)-3-(3-formyl-1-(4-methoxyphenyl)-1,2-dihydropyridin-2-yl)benzonitrile (30o):

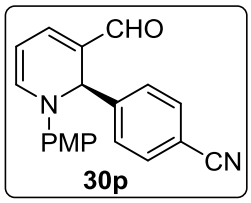


30o

Orange viscous liquid, (68 mg), 72% yield, $[\alpha]_D^{25}$ = – 67.6 (*c* 0.1, CH_2Cl_2, 84:16 er); IR (KBr)/cm^{-1} 2931, 2856, 2229, 1732, 1506, 1247, 1174; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.45 (t, *J* = 6.6 Hz, 1H), 6.25 (s, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.94 (d, *J* = 6.3 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.64–7.66 (m, 2H), 9.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.53, 57.96, 99.98, 112.52, 114.71 (2C), 118.74, 120.81 (2C), 122.82, 129.12, 129.49, 130.22, 131.35, 137.97, 139.95, 141.70, 143.11, 157.32, 188.93.; HRMS (ESI): $[MH^+]$ calcd for $[C_{20}H_{16}N_2O_2]$: 317.1290, found: 317.1298.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 80:20), 0.5 mL/min; major enantiomer t_R = 21.555 min, minor enantiomer t_R = 22.864 min.

(*R*)-4-(3-formyl-1-(4-methoxyphenyl)-1, 2-dihydropyridin-2-yl)benzonitrile (30p):

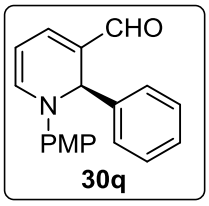


30p

Yellowish oily solid, (66 mg), 70% yield, $[\alpha]_D^{25}$ = – 56.4 (*c* 0.1, CH_2Cl_2, 94:6 er); IR (KBr)/cm^{-1} 2924, 2850, 2227, 1647, 1506, 1249, 1174; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.44 (t, *J* = 6.7 Hz, 1H), 6.27 (s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 6.3 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 6.0 Hz, 1H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.58 (d, *J* = 8.4 Hz, 2H), 9.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.51, 58.19, 100.00, 111.43, 114.62 (2C), 118.67, 120.69 (2C), 122.57, 126.25 (2C), 132.45 (2C), 137.91, 139.90, 141.84, 146.67, 157.24, 188.96; HRMS (ESI): $[MH^+]$ calcd for $[C_{20}H_{16}N_2O_2]$: 317.1290, found: 317.1292.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 80:20), 0.5 mL/min; minor enantiomer t_R = 27.835 min, major enantiomer t_R = 33.938 min.

(*R*)-1-(4-methoxyphenyl)-2-phenyl-1,2-dihydropyridine-3-carbaldehyde (30q):

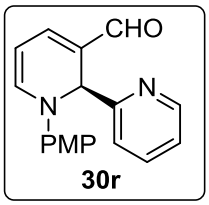


30q

Orange oily liquid, (57 mg), 66% yield, $[\alpha]_D^{25}$ = – 47.4 (*c* 0.3, CH_2Cl_2, 88:12 er); IR (KBr)/cm^{-1} 2925, 2851, 1680, 1505, 1240, 1178; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 5.42 (t, *J* = 6.6 Hz, 1H), 6.22 (s, 1H), 6.82 (d, *J* = 9.1 Hz, 2H), 6.90 (d, *J* = 6.2 Hz, 1H), 7.01 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 6.8 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 2H), 7.40 (d, *J* = 6.1 Hz, 1H), 7.45 (m, 1H), 9.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.50, 58.37, 93.76, 99.74, 114.45 (2C), 120.77(2C), 125.38 (2C), 127.65, 128.54 (2C), 129.96, 130.65, 139.96, 140.16, 156.95, 189.22; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{17}NO_2$]: 292.1337, found: 292.1342.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 85:15), 0.5 mL/min; minor enantiomer t_R = 12.215 min, major enantiomer t_R = 14.127 min.

(*S*)-1-(4-methoxyphenyl)-1,2-dihydro-[2,2'-bipyridine]-3-carbaldehyde (30r):

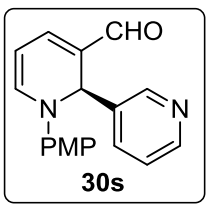


30r

Dark red pasty liquid, (58 mg), 67% yield, $[\alpha]_D^{25}$ = – 38.7 (*c* 0.2, CH_2Cl_2, 94:6 er); IR (KBr)/cm^{-1} 2924, 2854, 1674, 1596, 1342, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.42 (t, *J* = 6.6 Hz, 1H), 6.32 (s, 1H), 6.84 (d, *J* = 9.1 Hz, 2H), 7.00 (d, *J* = 6.1 Hz, 1H), 7.09 (d, *J* = 9.1 Hz, 2H), 7.15–7.22 (m, 2H), 7.40 (d, *J* = 7.8 Hz, 1H), 7.59–7.64 (m, 1H), 8.55 (d, *J* = 5.0 Hz, 1H), 9.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.48, 59.67, 99.68, 114.40 (2C), 120.69, 121.14 (2C), 122.00, 122.68, 136.79, 138.54, 140.77, 142.14, 149.02, 156.99, 159.67, 188.72; HRMS (ESI): [MH^+] calcd for [$C_{18}H_{16}N_2O_2$]: 293.1290, found:293.1293.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IB column (*n*-Hexane: *i*-PrOH = 80:20), 0.5 mL/min; minor enantiomer t_R = 14.159 min, major enantiomer t_R = 18.424 min.

(*R*)-1-(4-methoxyphenyl)-1,2-dihydro-[2,3'-bipyridine]-3-carbaldehyde (30s):



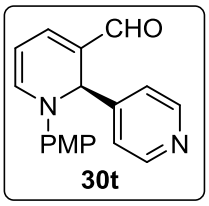
30s

Red oily solid, (62 mg), 71% yield, $[\alpha]_D^{25}$ = – 31.8 (*c* 0.1, CH_2Cl_2, 84:16 er); IR (KBr)/cm^{-1} 2924, 2852,1627, 1595, 1354, 1261, 1174; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 5.45 (t, *J* = 6.6 Hz, 1H), 6.25 (s, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 6.2 Hz, 1H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.20 (d, *J* = 6.7 Hz, 1H), 7.37 (m, 1H), 7.73–7.76 (m, 1H), 8.54 (dd, *J* = 4.9 Hz, *J* = 2.2 Hz, 1H), 8.65 (d, *J* = 2.2 Hz, 1H), 9.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.51, 56.73, 99.83, 114.65 (2C), 120.96,

122.84, 123.58, 127.27, 133.69, 137.15, 138.04, 140.09, 141.65, 146.92, 148.86, 157.25, 188.81; HRMS (ESI): [MH^+] calcd for [$C_{18}H_{16}N_2O_2$]: 293.1290, found: 293.1288.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 25.981 min, major enantiomer t_R = 32.048 min.

(*R*)-1-(4-methoxyphenyl)-1, 2-dihydro-[2,4'-bipyridine]-3-carbaldehyde (30t)

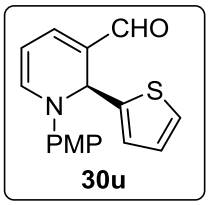


30t

Reddish pasty liquid, (64 mg), 73% yield, $[\alpha]_D^{25}$ = – 29.5 (*c* 0.1, CH_2Cl_2, 92:8 er); IR (KBr)/cm^{-1} 2924, 2850,1645, 1595, 1504, 1249, 1174; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.46 (t, *J* = 6.7 Hz, 1H), 6.25 (s, 1H), 6.85 (d, *J* = 9.1 Hz, 2H), 6.94 (d, *J* = 6.3 Hz, 1H), 6.97 (d, *J* = 9.2 Hz, 2H), 7.23 (d, *J* = 6.5 Hz, 1H), 7.31 (d, *J* = 6.8 Hz, 2H), 8.54 (d, *J* = 6.7 Hz, 2H), 9.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.47, 57.40, 100.29, 114.57 (2C), 120.51 (2C), 120.63 (2C), 121.98, 137.79, 139.72, 141.96, 149.43 (2C), 150.43, 157.17, 188.93; HRMS (ESI): [MH^+] calcd for [$C_{18}H_{16}N_2O_2$]: 293.1290, found: 293.1296.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 31.021 min, major enantiomer t_R = 38.858 min.

(*S*)-1-(4-methoxyphenyl)-2-(thiophen-2-yl)-1,2-dihydropyridine-3-carbaldehyde (30u):

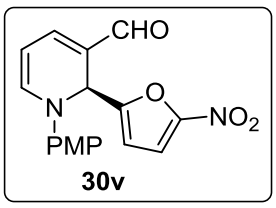


30u

Reddish viscous oil, (59 mg), 67% yield, $[\alpha]_D^{25}$ = – 23.2 (*c* 0.2, CH_2Cl_2, 88:12 er); IR (KBr)/cm^{-1} 2926, 2855, 1686, 1509, 1348, 1176; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 5.47 (t, *J* = 6.5 Hz, 1H), 6.42 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 2H), 6.88–6.90 (m, 1H), 6.95 (d, *J* = 6.2 Hz, 1H), 6.88 (d, *J* = 3.0 Hz, 1H), 7.06–7.14 (m, 4H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.89, 55.26, 99.68, 114.32 (2C), 120.82 (2C), 123.70, 124.10, 126.28, 135.02, 136.34, 137.86, 139.33, 140.94, 156.84, 188.21; HRMS (ESI): [MH^+] calcd for [$C_{17}H_{15}NO_2S$]: 298.0901, found: 298.0985.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 25.069 min, major enantiomer t_R = 30.734 min.

(*S*)-1-(4-methoxyphenyl)-2-(5-nitrofuran-2-yl)-1,2-dihydropyridine-3-carbaldehyde (30v):



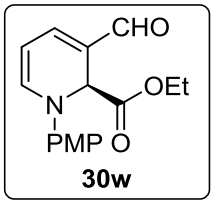
30v

Dark red viscous liquid, (69 mg), 71% yield, $[\alpha]_D^{25}$ = – 37.5 (*c* 0.1, CH_2Cl_2, 87:13 er); IR (KBr)/cm^{-1} 2924, 2854,1674, 1596, 1342, 1172; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 5.53 (t, *J* = 6.5 Hz, 1H), 6.32 (s, 1H), 6.39 (d, *J* = 6.5 Hz, 1H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.95–6.98 (m, 1H), 7.15 (d, *J* = 6.5 Hz, 1H), 7.20–7.23 (m, 3H), 9.44 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

52.92, 55.57, 100.63, 110.80, 112.22, 114.78 (2C), 118.53, 121.81 (2C), 137.70, 139.69, 142.31 (2C), 156.25, 157.55, 187.80; HRMS (ESI): [MH^+] calcd for [$C_{17}H_{14}N_2O_5$]: 327.0981, found: 327.0989.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IA column (*n*-Hexane: *i*-PrOH = 80:20), 0.5 mL/min; major enantiomer t_R = 25.794 min, minor enantiomer t_R = 27.856.

(*S*)-ethyl3-formyl-1-(4-methoxyphenyl)-1,2-dihydropyridine-2-carboxylate (30w):

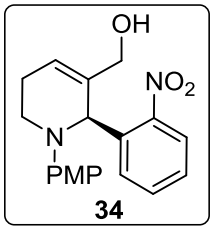


30w

Yellow solid, (75 mg), 87% yield, (Melting Point) = 108–111^oC); $[\alpha]_D^{25}$ = – 48.7 (*c* 0.1, CH_2Cl_2, >99.05:0.5 er); IR (KBr)/cm^{-1} 2923, 2850, 1673, 1592, 1340, 1170; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, *J* = 7.1 Hz, 3H), 3.79 (s, 3H), 4.16 (q, *J* = 7.1 Hz, 2H), 5.47 (t, *J* = 6.7 Hz, 1H), 5.78 (s, 1H), 6.88 (d, *J* = 9.1 Hz, 2H), 7.01–7.04 (m, 2H), 7.08 (d, *J* = 9.1 Hz, 2H), 9.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.00, 55.46, 56.92, 61.61, 100.27, 114.42 (2C), 118.09, 121.27 (2C), 137.99, 140.08, 141.27, 157.14, 170.51, 187.80; HRMS (ESI): [MH^+] calcd for [$C_{16}H_{17}NO_4$]: 288.1236, found: 288.1240.

Enantiomeric ratio was determined by HPLC with a Chiralpak-IB column (*n*-Hexane: *i*-PrOH = 92:8), 0.5 mL/min; minor enantiomer t_R = 34.556 min, major enantiomer t_R = 39.685 min.

(*R*)-(1-(4-methoxyphenyl)-2-(2-nitrophenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (34):



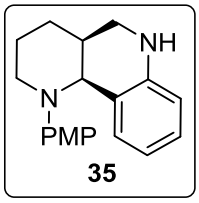
34

To the stirred solution of compound **30a** (200 mg, 0.59 mmol) in CH_3OH (3.0 mL) and CH_3CO_2H (100 mol%) at 0 ^oC was added $NaBH_4$ portion wise till the complete consumption of starting martial by TLC. This reaction was further stirred at rt for additional 2 hrs. Reaction mixture was then stirred with saturated $NaHCO_3$ (5.0 ml) and EtOAc (5.0 mL) for 1 hr. Organic layer was separated and aqueous layer was next extracted with EtOAc (2 x 5.0 mL) and combined organic layer was evaporated under vacuo. Purification was performed by a silica gel column and eluted with hexane/EtOAc) to give product **34** (168 mg, 85% yield).

Yellow viscous oil, $[\alpha]_D^{25}$ = – 81.4 (*c* 0.1, CH_2Cl_2); IR (KBr)/cm^{-1} 3448, 2924, 2854,1520, 1466, 1350, 1242, 1180, 1034; ^1H NMR (400 MHz, $CDCl_3$) δ 1.77–1.79 (bs, 1H), 2.18–2.23 (m, 1H), 2.25–2.32 (m, 1H), 3.00–3.07 (m, 1H), 3.15–3.19 (m, 1H), 3.73 (s, 3H), 4.06 (s, 2H), 5.80 (s, 1H), 6.16 (t, *J* = 4.3 Hz, 1H), 6.72 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 7.32–7.36 (m, 1H), 7.50–7.51 (m, 2H), 7.63 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.70, 44.50, 55.35, 55.57, 64.91, 114.20 (2C), 121.40 (2C), 124.16, 125.61, 128.02, 130.13, 131.66,

135.19, 136.73, 143.78, 150.57, 154.65; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{20}N_2O_4$]: 341.1501, found: 341.1506.

(4a*S*, 10b*S*)-1-(4-methoxyphenyl)-1,2,3,4,4a,5,6,10b-octahydrobenzo[*h*][1,6]naphthyridine (35):



35

To a stirred solution of compound **34** (120 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added Et_3N (3.0 equiv, 1.06 mmol) at rt. Reaction was taken to 0 ^oC and TsCl (100 mg, 0.53 mmol) in CH_2Cl_2 was added drop and then stirred at rt for additional 4 hr. Progress of the reaction was monitored by TLC. Reaction was stirred with NH_4Cl (20% sol., 5 mL) and extracted with additional CH_2Cl_2 (5 mL). The combined organic layer was washed with brine solution and concentrate under vacuo to give crude (~180 mg) solid mass. This was used further for next step without purification at this stage. This crude mass taken in dry methanol (4 mL) and added 10% by weight of 10% Pd/C. The reaction mixture was purged with H_2 and stirred under H_2 at room temperature for 8 hours and monitored by TLC. Reaction mixture was filtered through celite and washed the celite with methanol. The organic layer was evaporated under vacuo and purified through silica gel column chromatography using Hexane/EtOAc to afford **35** (68 mg) in 65% yields in two steps.

Colorless oily soild, $[\alpha]_D^{25}$ = – 14.4 (*c* 0.1, CH_2Cl_2); IR (KBr)/cm^{-1} 3448, 3040, 2924, 2854, 1736, 1512, 1458, 1250, 1041, 810, 748; ^1H NMR (400 MHz, $CDCl_3$) δ 1.75–1.81 (m, 2H), 2.23–2.28 (m, 2H), 2.44–2.49 (m, 2H), 2.58–2.62 (m, 1H), 3.18 (m, 3H), 3.76 (s, 3H), 4.08 (d, *J* = 1.0 Hz, 1H), 6.62 (d, *J* = 9.1 Hz, 1H), 6.69 (d, *J* = 9.0 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.96–7.00 (m, 2H), 7.15 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.30, 24.54, 31.50, 42.16, 46.57, 55.77, 56.73, 113.63, 114.83 (2C), 115.98, 117.02, 120.14, 127.62 (2C), 128.09, 144.82, 145.65, 151.66; HRMS (ESI): [MH^+] calcd for [$C_{19}H_{22}N_2O$]: 295.1810, found: 295.1816.

3.8 Gram scale synthesis of 1,2-DHPs 30c and *ent*-30c:

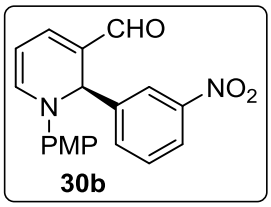
Glutaraldehyde **27** (25 % in water, 4.6 mL, 11.7 mmol) was added to a mixture of preformed *N*-PMP imine **28c** (1.0 g, 3.9 mmol) and L-Proline **29** (90 mg, 0.78 mmol) in DMSO (30 mL) at 10 ^oC. The reaction mixture was further stirred at the same temperature until the imine was consumed as monitored by TLC. IBX (1.2 equiv, 4.68 mmol) was added into the same flask and further heated at 40 ^oC for 4 hrs. Reaction was quenched with $NaHCO_3$ (20 % aq solution). The aqueous layer was extracted with ethyl acetate (2 × 30 mL). The combined organic layers were washed with brine once and dried over anh. Na_2SO_4 and concentrated in vacuo. Purification was

performed by a silica gel column and eluted with hexane/EtOAc to give product **30c** (1.06 g, 81% yield). The enantiomeric ratios (er) of the products were determined by stationary chiral phase HPLC analysis.

3.9 Crystal structure data for (30b) and (30w)

(*R*)-1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1,2-dihydropyridine-3-carbaldehyde (**30b**):

(CCDC No. 1403679)



30b

The title compound (*R*)-1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1,2-dihydropyridine-3-carbaldehyde (**30b**), $C_{19}H_{16}N_2O_4$, crystallizes in the orthorhombic space group P 2_1 2_1 2_1 with the unit-cell parameters: a= 7.0624(7), b= 7.6001(6), c= 29.924(2) Å and Z = 4. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data collected at room temperature and refined by full-matrix least-squares procedures to a final R-value of 0.0424 for 1292 observed reflections.

Crystal structure determination and refinement

X-ray intensity data of 4320 reflections (of which 1854 unique) were collected on *X'calibur* CCD area-detector diffractometer equipped with graphite monochromated MoKα radiation (λ = 0.71073 Å). The crystal used for data collection was of dimensions 0.30 x 0.20 x 0.20 mm. The cell dimensions were determined by least-squares fit of angular settings of 1247 reflections in the θ range 3.85 to 24.85^o**.** The intensities were measured by ω scan mode for θ ranges 3.53 to 26.00^o. 1252 reflections were treated as observed (I > 2σ(I)). Data were corrected for Lorentz, polarisation and absorption factors. The structure was solved by direct methods using SHELXS97 [1]. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97 [1]. The final refinement cycles converged to an R = 0.0424 and wR (F^2) = 0.0631 for the observed data. Residual electron densities ranged from -0.179< Δρ < 0.139 eÅ^{-3}. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in Table 1. The geometry of the molecule was calculated using the WinGX [3], PARST [4] and PLATON [5] software's.

Table 3.3 Crystal and experimental data (**30b**)

CCDC No.	**1403679**
Crystal description	white block
Crystal size	0.3 X 0.2 X 0.2 mm
Empirical formula	$C_{19}H_{16}N_2O_4$
Formula weight	336.34
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a= 7.0624(7), b= 7.6001(6), c= 29.924(2) Å
Crystal system	orthorhombic
Space group	P 2_1 2_1 2_1
Unit cell volume	1606.2(2)
No. of molecules per unit cell, Z	4
Temperature	293(2) K
Absorption coefficient	0.099 mm^{-1}
F(000)	704
Scan mode	ω scan
θ range for entire data collection	3.53 <θ< 26.00
Range of indices	h= -8 to 7, k= -9 to 5, l= -17 to 36
Reflections collected / unique	4320 / 1854
Reflections observed (I > 2σ(I))	1292
R_{int}	0.0322
R_{sigma}	0.0640
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	227
Final R	0.0424
wR(F^2)	0.0631
Weight	$1/[\sigma^2(F_o^2)+(0.0188P)^2+0.0000P]$ Where $P=[F_o^2+2F_c^2]/3$
Goodness-of-fit	0.978
Final residual electron density	$-0.179 < \Delta\rho < 0.139$ eÅ^{-3}
Measurement	*X'calibur system-Oxford diffraction make, U.K*
Software for structure solution:	SHELXS97 (Sheldrick, 2008)
Software for refinement:	SHELXL97 (Sheldrick, 2008)
Software for molecular plotting:	ORTEP-3 (Farrugia, 1997) PLATON
Software for geometrical calculation	PLATON (Spek, 2009) PARST (Nardelli, 1995)

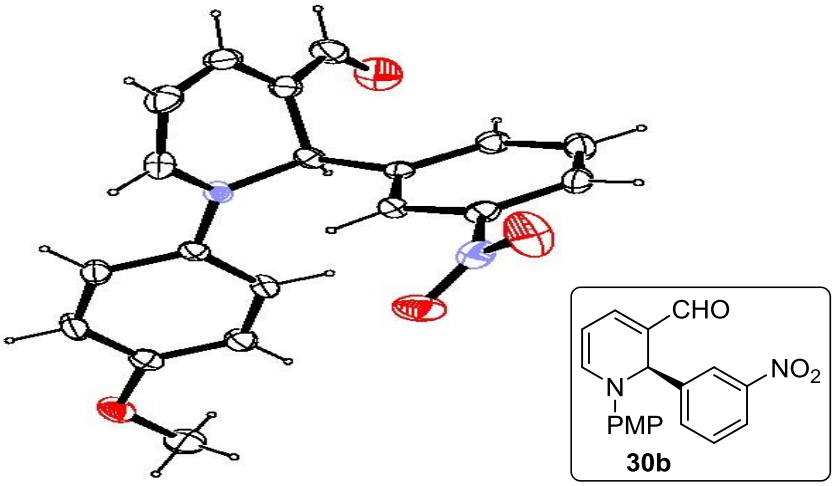
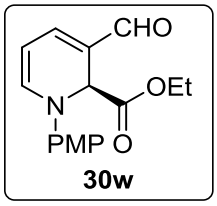


Figure 3.4 *ORTEP* view of the molecule (**30b**)

(*S*)-ethyl3-formyl-1-(4-methoxyphenyl)-1,2-dihydropyridine-2-carboxylate (30w): (CCDC No. 1401085)



The title compound (*S*)-ethyl3-formyl-1-(4-methoxyphenyl)-1,2-dihydropyridine-2-carboxylate (**30w**), $C_{16}H_{17}NO_4$, crystallizes in the orthorhombic space group P 2_1 2_1 2_1 with the unit-cell parameters: a= 7.8684(9), b= 9.5941(9), c= 20.0066(15) Å and Z = 4. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data collected at room temperature and refined by full-matrix least-squares procedures to a final R-value of 0.0585 for 974 observed reflections.

Crystal structure determination and refinement

X-ray intensity data of 3947 reflections (of which 1720 unique) were collected on *X'calibur* CCD area-detector diffractometer equipped with graphite monochromated MoKα radiation (λ = 0.71073 Å). The crystal used for data collection was of dimensions 0.30 x 0.20 x 0.20 mm. The cell dimensions were determined by least-squares fit of angular settings of 1024 reflections in the θ range 3.91 to 23.94^o**.** The intensities were measured by ω scan mode for θ ranges 3.50 to 26.00^o. 974 reflections were treated as observed (I > 2σ(I)). Data were corrected for Lorentz, polarisation and absorption factors. The structure was solved by direct methods using SHELXS97 [1]. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97 [1]. The final refinement cycles converged to an R = 0.0585 and wR (F^2) = 0.1373 for the observed data. Residual electron

Table 3.4 Crystal and experimental data **30w**

CCDC No.	**1401085**
Crystal description	white block
Crystal size	0.3 X 0.2 X 0.2 mm
Empirical formula	$C_{16}H_{17}NO_4$
Formula weight	287.31
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a= 7.8684(9), b= 9.5941(9), c= 20.0066(15) Å
Crystal system	orthorhombic
Space group	P 2_1 2_1 2_1
Unit cell volume	1510.3(3)
No. of molecules per unit cell, Z	4
Temperature	293(2) K
Absorption coefficient	0.091 mm^{-1}
F(000)	608
Scan mode	ω scan
θ range for entire data collection	3.50 <θ< 26.00
Range of indices	h= -9 to 8, k= -11 to 7, l= -23 to 24
Reflections collected / unique	3947 / 1720
Reflections observed (I > 2σ(I))	974
R_{int}	0.0360
R_{sigma}	0.0630
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	192
Final R	0.0585
wR(F^2)	0.1373
Weight	$1/[\sigma^2(F_o^2)+(0.0840P)^2+0.0000P]$ Where $P=[F_o^2+2F_c^2]/3$
Goodness-of-fit	0.981
Final residual electron density	$-0.237< \Delta\rho < 0.178$ eÅ^{-3}
Measurement	*X'calibur system-Oxford diffraction make, U.K*
Software for structure solution:	SHELXS97 (Sheldrick, 2008)
Software for refinement:	SHELXL97 (Sheldrick, 2008)
Software for molecular plotting:	ORTEP-3 (Farrugia, 1997) PLATON
Software for geometrical calculation	PLATON (Spek, 2009) PARST (Nardelli, 1995)

densities ranged from $-0.237 < \Delta\rho < 0.178$ eÅ^{-3}. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4). The crystallographic data are summarized in Table 2.

An ORTEP view of the compound with atomic labeling is shown in Fig. 2 [2]. The geometry of the molecule was calculated using the WinGX [3], PARST [4] and PLATON [5] software's.

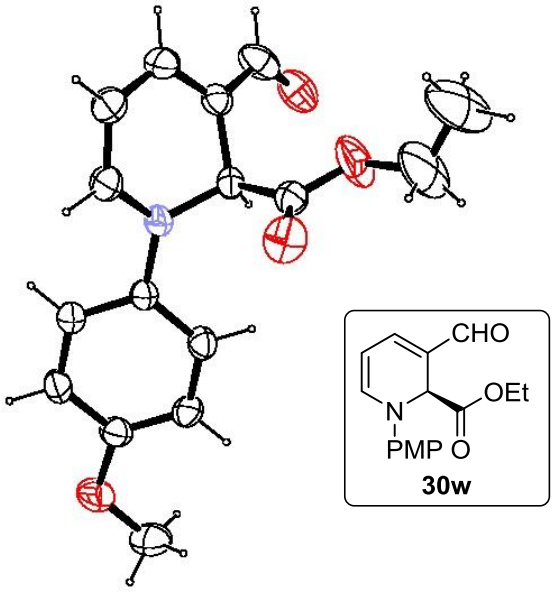


Figure 3.5 *ORTEP* view of the molecule (**30w**)

References for crystal data:

1. Sheldrick GM (2008) Acta Cryst A64: 112
2. Farrugia LJ (1997) J Appl Cryst 30:565
3. Farrugia LJ (1999) J Appl Cryst 32:837
4. Nardelli M (1995) J Appl Cryst 28:659
5. Spek AL (2009) Acta Cryst D65: 148–155

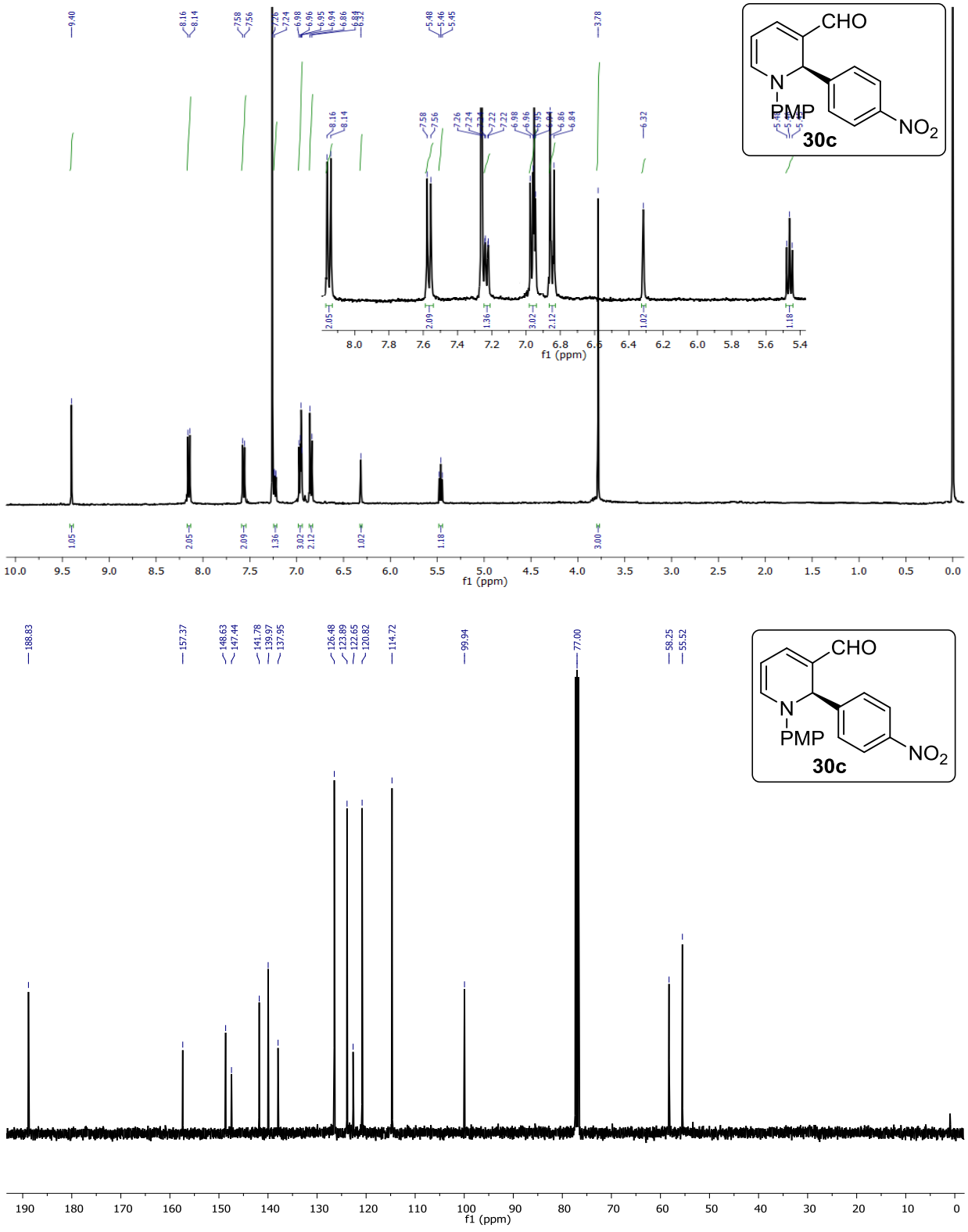
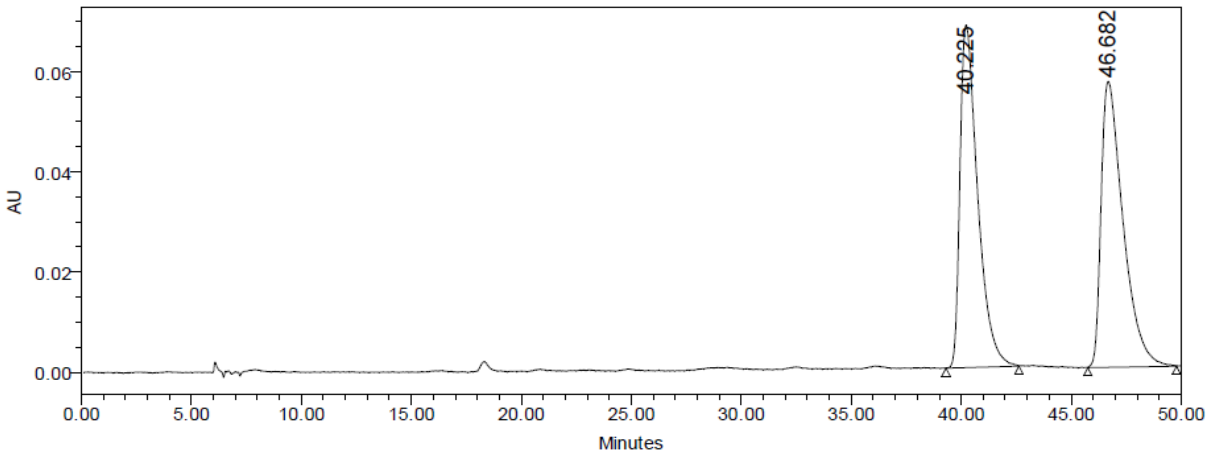


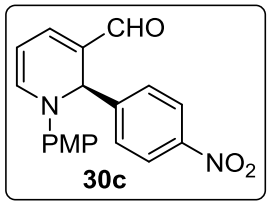
Figure 3.6 ^{1}H and ^{13}C NMR spectra of **30c**



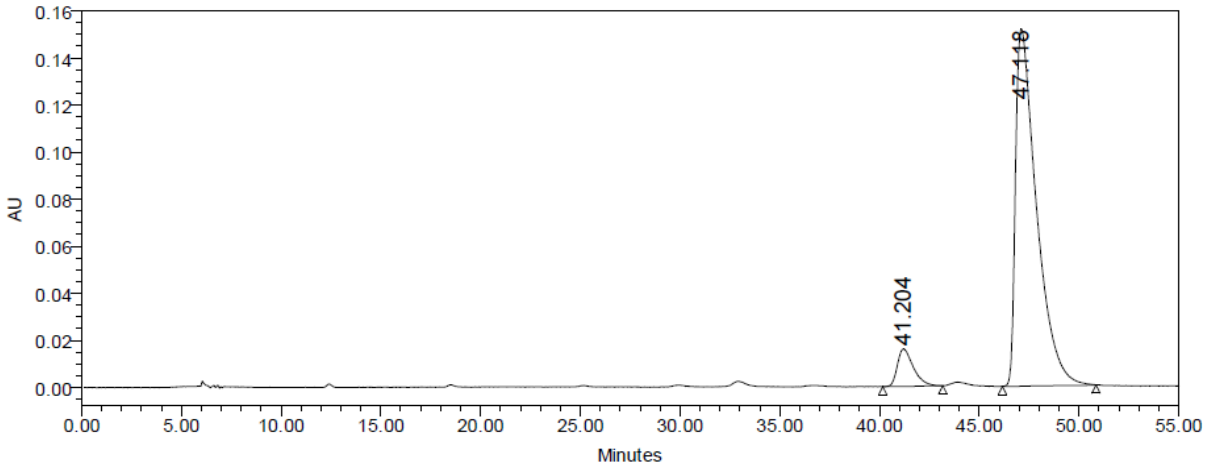
Channel: 2998; Processed Channel: PDA 380.0 nm; Result Id: 4689; Processing Method: 4 NO2 RACEMIC 1 2 DHP

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	40.225	3817605	49.09	68317
2	PDA 380.0 nm	46.682	3958677	50.91	57048



30c

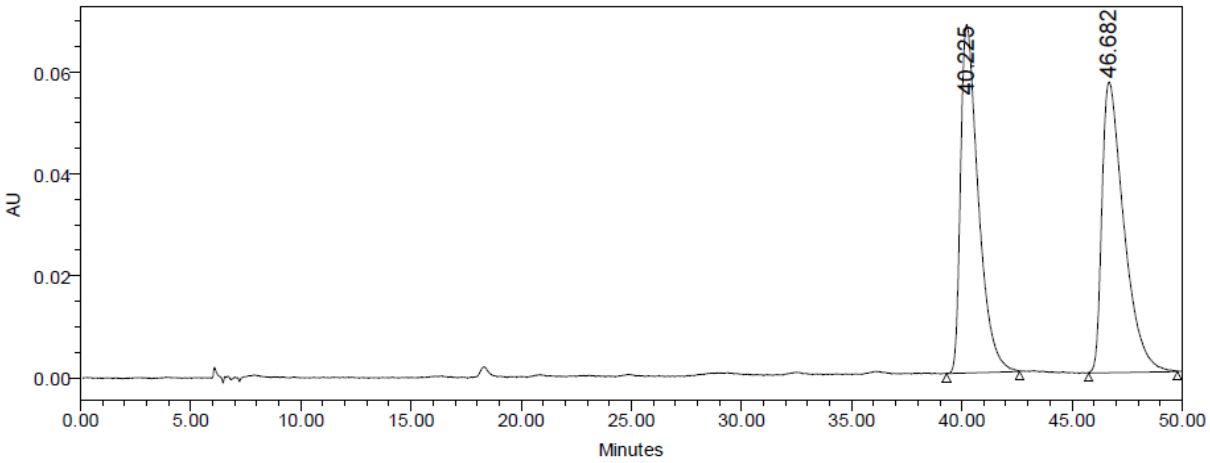


Channel: 2998; Processed Channel: PDA 380.0 nm; Result Id: 4687; Processing Method: 4 NO2 1 2 DHP L PROLINE

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	41.204	881947	7.37	15903
2	PDA 380.0 nm	47.118	11091753	92.63	151748

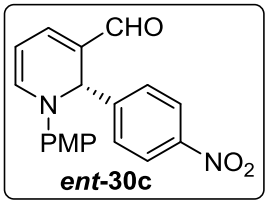
Figure 3.7 HPLC chromatogram of **30c**



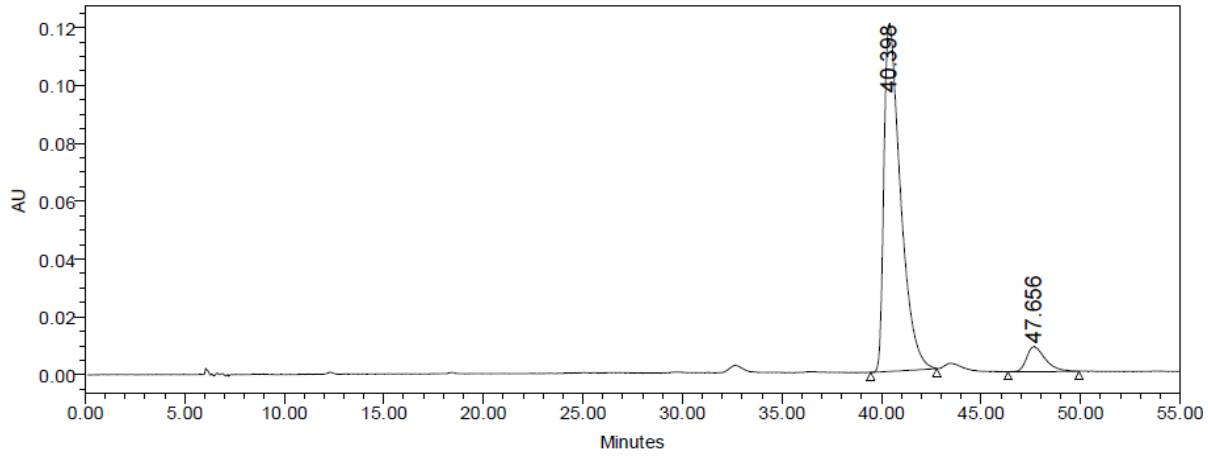
Channel: 2998; Processed Channel: PDA 380.0 nm; Result Id: 4689; Processing Method: 4 NO2 RACEMIC 1 2 DHP

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	40.225	3817605	49.09	68317
2	PDA 380.0 nm	46.682	3958677	50.91	57048



***ent*-30c**



Channel: 2998; Processed Channel: PDA 380.0 nm; Result Id: 4681; Processing Method: 4 nitro 1 2 DHP D proline

Processed Channel Descr.: PDA 380.0 nm

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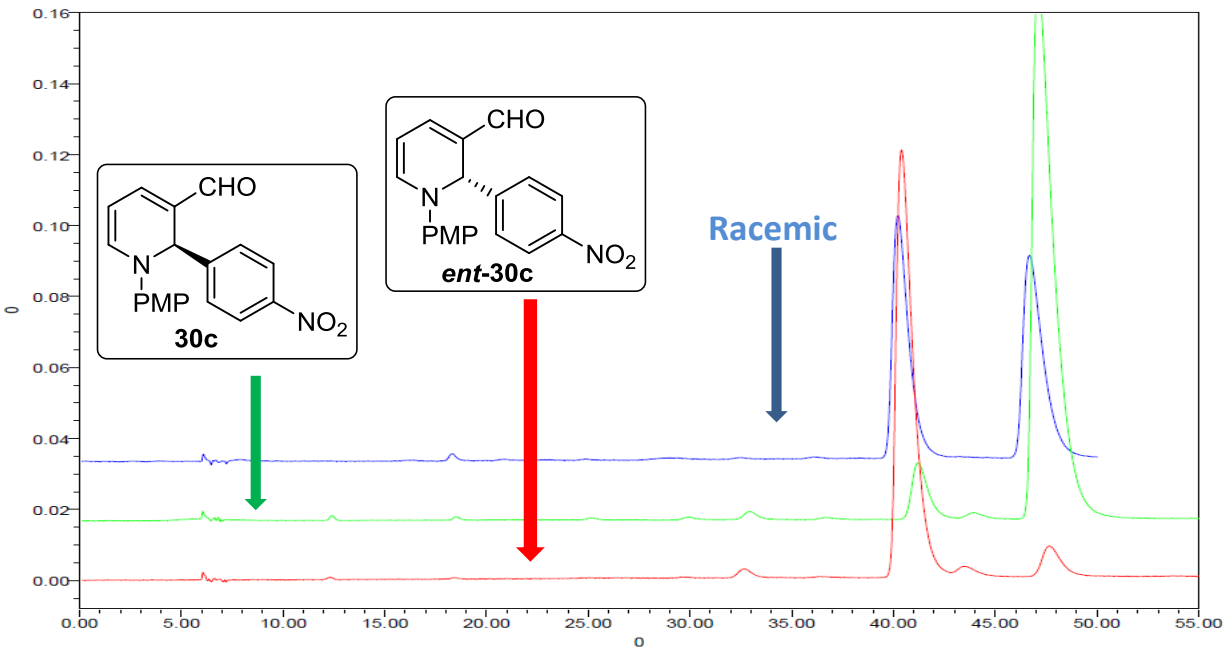
1	PDA 380.0 nm	40.398	6956192	92.43	120098
2	PDA 380.0 nm	47.656	570104	7.57	8656

Empower 2 software

Overlay Report



Racemic **30c**

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	40.225	3817605	49.09	68317
2	PDA 380.0 nm	46.682	3958677	50.91	57048

Chiral (-)-**30c** (L-Proline was used as catalyst)

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	41.204	881947	7.37	15903
2	PDA 380.0 nm	47.118	11091753	92.63	151748

Chiral (+)-*ent*-**30c** (D-Proline was used as catalyst)

Processed Channel Descr.: PDA 380.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 380.0 nm	40.398	6956192	92.43	120098
2	PDA 380.0 nm	47.656	570104	7.57	8656

Figure 3.8 HPLC chromatogram of **30c** and ent-**30c**

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Chapter - 4

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

4.1 Introduction:

The innovation of a new environmentally benign chemical transformation, targeting to preserve the environmental profile by reducing the waste levels, high incorporation of the starting materials into the final products with conserving time and energy, is not only considered as a sustainable synthetic strategy, but also support the foundation of the green chemistry philosophy. In this direction, the development of "one-pot domino process" for chemical transformations that run in a single flask with the ultimate aim "to complete an entire multi-step, multi-reaction synthesis in a single pot" is a current ambition in organic synthesis.[1-6] One way to achieve this task is to add catalysts and reagents sequentially at different time intervals, without workup and product isolation at any intermediate stage. These kinds of green protocols can effectively save time, solvents as well as materials used in chromatographic purification. The synthetic approaches increasing the "pot economy" of the overall process are highly desirable.[7-9] In addition, multi-component reactions (MCRs) is an alternative way to achieve a similar objective of multiple bond formation in one pot reactions.[10-14] These two approaches are undoubtedly the common platforms for rapid construction of many complex molecules in quite an economical way, however, the development of their asymmetric variant is still infancy [15-19] and their exploration is highly desirable due to the increasing need of chiral scaffolds in pharmaceuticals. In this direction, organocatalysis [20-26] has emerged as a major contributor in the recent growth of asymmetric multi-component,[27-30] and domino reactions,[31-36] with its various modes of activations under mild reaction conditions. This metal-free catalysis acts as an ideal toolbox in the search for practically simple and efficient asymmetric organic transformations to construct structurally, stereo chemically multifaceted architectures in a single synthetic operation.

On the other hand, functionalized piperidine and polyhydropyridines are an integral part of numerous natural products.[37-43] The development of new methods to synthesize nitrogen-containing medium-sized ring systems is still an interesting area of research in organic chemistry. In particular, 1,2,5,6-tetrahydropyridine (THP) is an important structural motif present in many biologically important synthetic pharmaceuticals as well as natural products.[44-48] The development of catalytic asymmetric approaches for the construction of these molecules in optically active forms remains an attractive area in organic synthesis. Some of the medicinally important representative examples are shown in **Figure 4.1**.

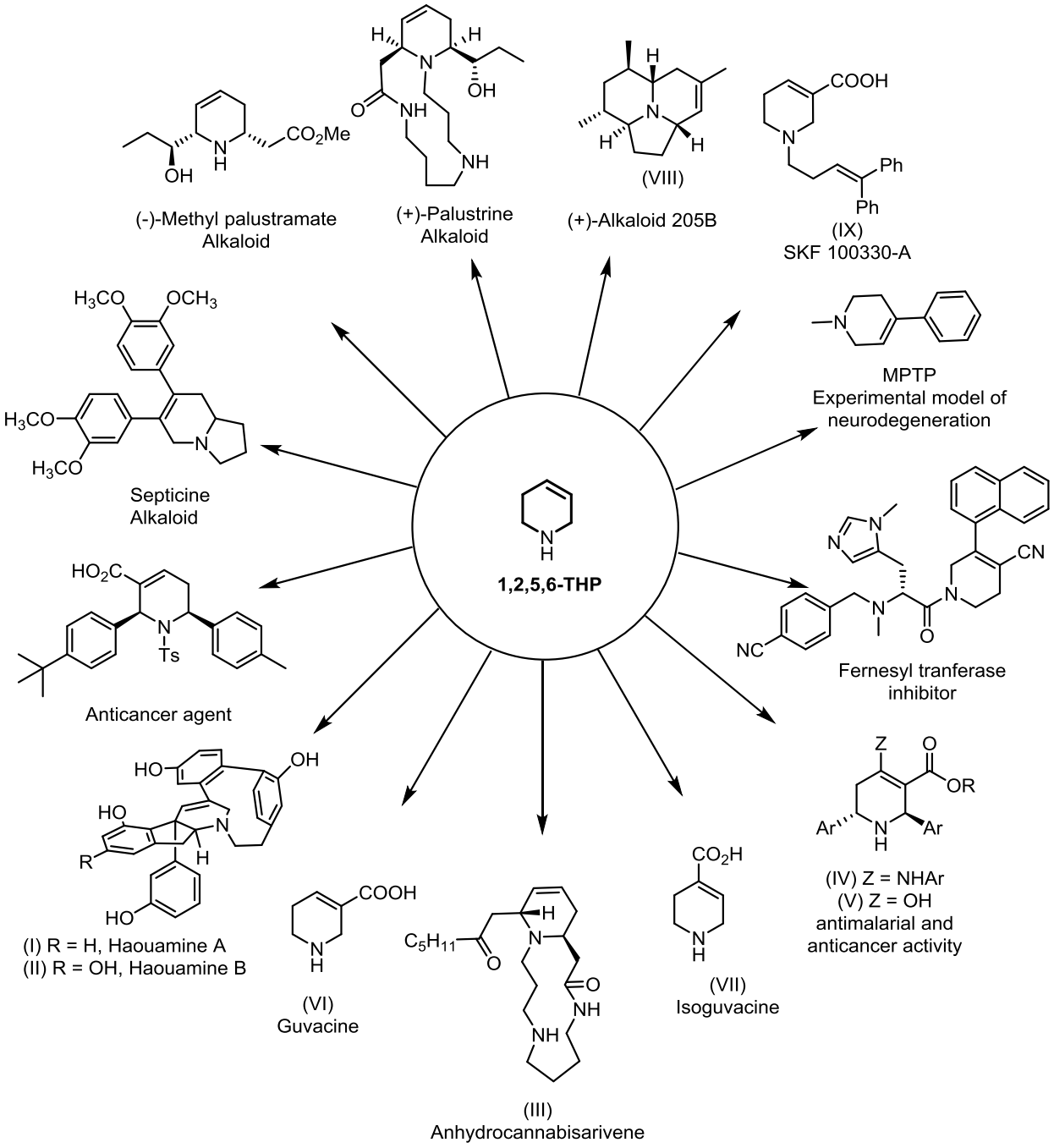
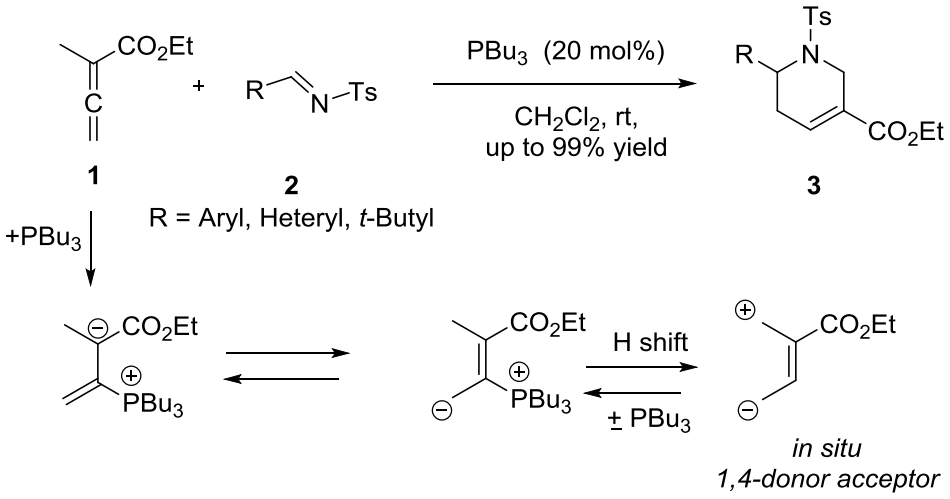


Figure 4.1 Biologically important compounds containing 1,2,5,6-tetrahydropyridine (THP) skeleton

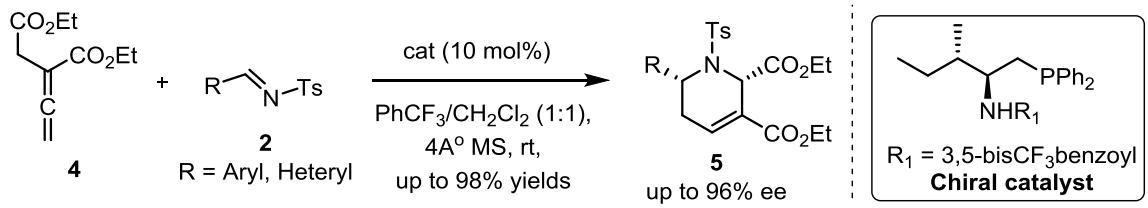
Tetrahydropyridines are the important common skeletons found in huge number of alkaloids. [97, 98, 100] These compounds are also used as anticancer drugs, [101] and potent agonists in the neurological systems.[59, 62] Recently, synthetic compounds (IV and V) and other similar scaffolds in **figure 4.1** are recognized as antimalarial and anti-cancer agents. [49-51] Due to the medicinal importance of the aforementioned scaffold, several attractive methods found in the literature for the synthesis of 1,2,5,6-THPs[52,53] which includes, (a) Hetero-Diels-Alder reactions,[54-58] (b) Catalytic asymmetric Diels-Alder reactions involving imines [59-62] and (c) Ring closing metathesis (RCM).[63-69]

(a) Hetero-Diels-Alder reactions are often performed with allenes **1** as 1,4-carbon *donor-acceptor* with N-tosyl imines **2** for the construction of tetrahydropyridines **3** exemplified in **scheme 4.1.** This method was a phosphine catalyzed [4+2] Hetero-Diels-Alder reaction afforded racemic THPs **3**.



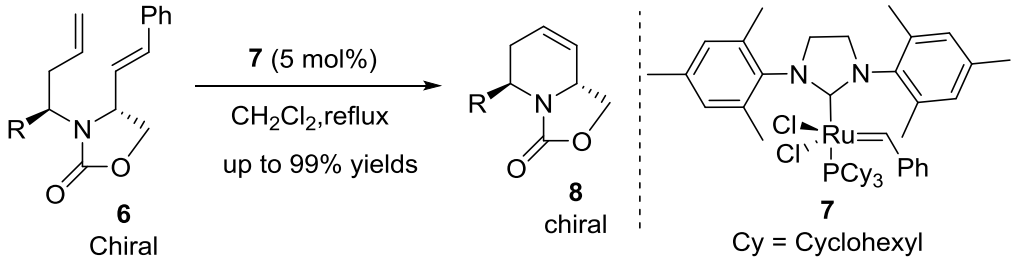
Scheme 4.1 Hetero Diels-Alder [4+2] cycloaddition approach for 1,2,5,6-THPs[58]

(b) Catalytic asymmetric Diels-Alder reactions involving imine are explored up to some extent in the literature for the asymmetric synthesis of tetrahydropyridines. These strategies adopted allenes **4** as 1,4-carbon *donor-acceptors* with imines **2**, in presence of a chiral catalyst produced the chiral tetrahydropyridines **5** exemplified in **Scheme 4.2.**



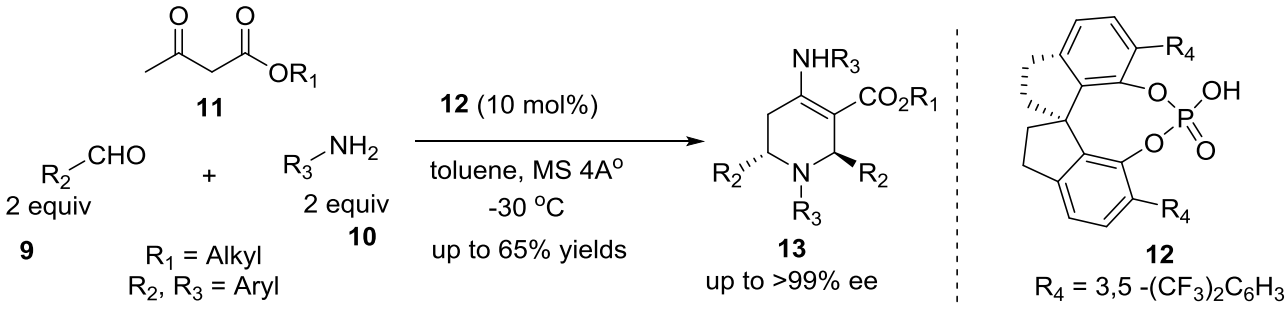
Scheme 4.2 Asymmetric Hetero Diels-Alder [4+2] cycloaddition approach for THPs [62]

(c) Ring closing metathesis (RCM) reactions are also known in the literature for the construction of tetrahydropyridine ring systems. But, synthesis of starting materials for the RCM reactions required several steps and tedious procedures. Chirality induced terminal olefins **6** which are very difficult to access, was the main dis advantage of this methodology.



Scheme 4.3 Ring closing metathesis (RCM) for the synthesis of 1,2,5,6-THPs [68]

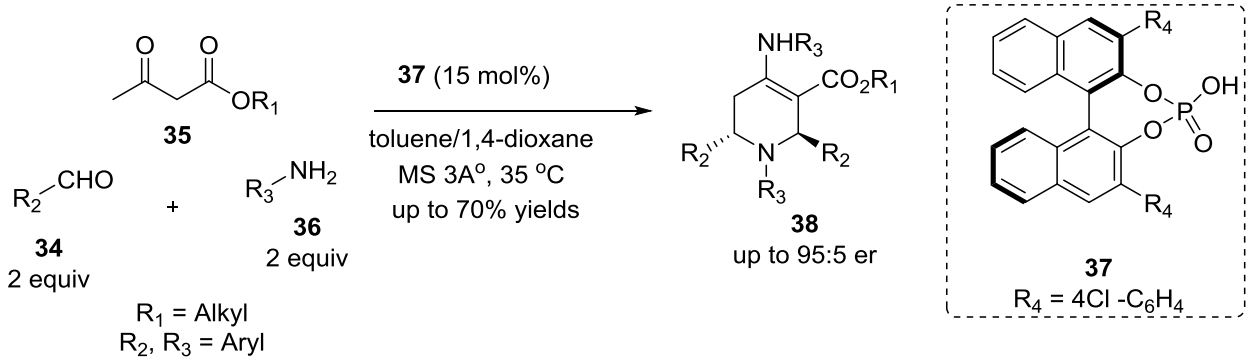
Besides other reports on the asymmetric synthesis of 1,2,5,6-THPs, [70-73] the development of multi-component synthetic strategies for optically pure THPs under environment-friendly organocatalytic conditions is still important. In this direction, a chiral phosphoric acid catalyzed MCR involves aromatic aldehydes, anilines, and β-ketoesters to obtain enantio enriched 1,2,5,6-THPs with a high level of stereo control was reported by Xufeng Lin *et al*. [74] This multi component reaction (MCR) strategy involved the condensation of amine **10** with keto group of ethyl acetoacetate **11** (EAA) forming imine followed by enamine and further condensation of active methylene group of EAA with aldehyde **9** formed in situ diene which further underwent Hetero Diels-Alder reaction with *in situ* generated imine from aldehyde **9** and amine **10** produced the highly functionalized 1,2,5,6-tetrahydropyridine scaffolds **13** which have shown a very good antimalarial activities (**scheme 4.4**).



Scheme 4.4 Multicomponent approach for the synthesis of chiral THPs

While, a similar approach was independently reported by Shi and Tu *et al*., at the very same time where they have used a different chiral phosphoric acid as a catalyst as shown in **Scheme 4.5**.[75]

This methodology involved as a chiral phosphoric acid catalyzed condensation (EAA) **11** with the aryl aldehyde **9** followed by Mannich reaction with the *in situ* generated imine and consequent cyclization produced the chiral 1,2,5,6-THPs **13**.

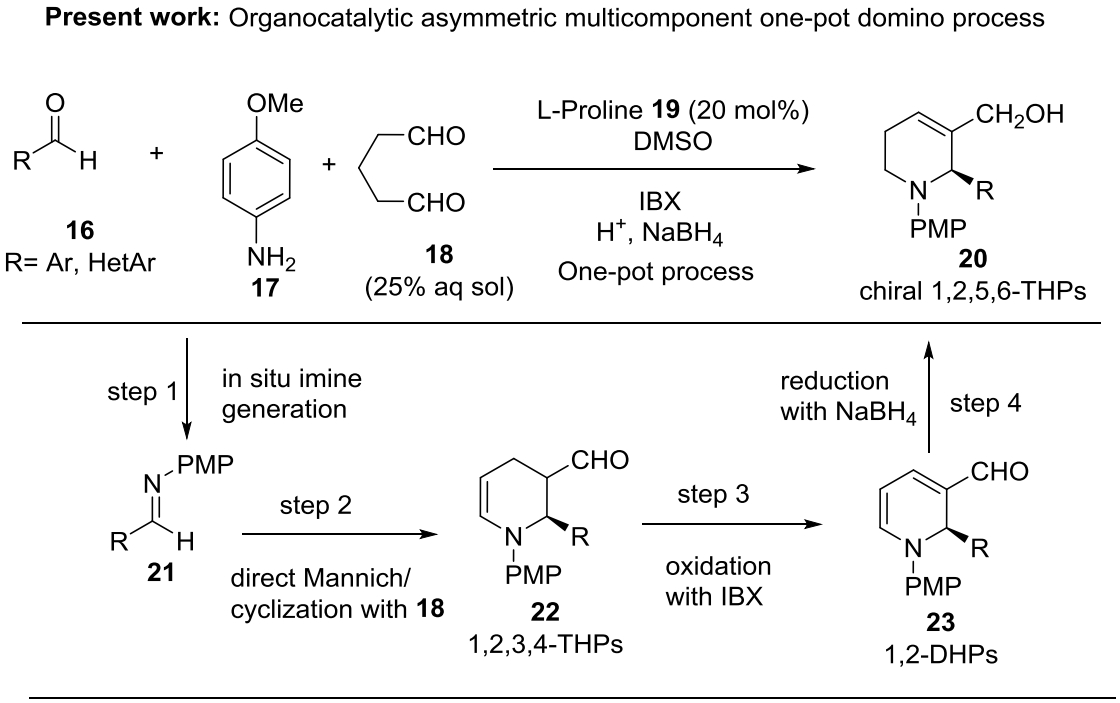


Scheme 4.5 Multicomponent enantioselective approach for chiral 1,2,5,6-THPs

A multi-component reaction will be more cost-effective by linking through a domino-process of three or even four consecutive steps in one pot operation in such a way that the product of initial step later becomes the substrate for next reaction until the process leads to stable product. However, the exact knowledge of the mechanisms and possibilities of the singular reaction steps is necessary for the development of such domino-process. Therefore, the main objective of present work is to assemble Proline-catalytic multi-component reaction with domino-process of sequential oxidation-reduction in the same flask to synthesize 1,2,5,6-tetrahydropyridine (THPs) with high stereo selectivity **(Scheme 4.6)**

Linear dialdehydes have been recently reviewed as suitable bifunctionalized substrates for aminocatalyzed transformations in asymmetric and non-asymmetric fashion to synthesize various carbo- and heterocyclic compounds.[76,77] Our group has recently developed amine catalyzed [4+2] annulation between glutaraldehyde and imines for the synthesis of chiral piperidines,[78] and also for the synthesis of optically active 1,2-dihydropyridines **23** (DHPs) (Scheme **4.6**).[79] Next, we extend our idea for the synthesis of 1,2,5,6-THPs and that is quite feasible if we selectively reduce the in situ generated 1,2-DHPs without isolation so that a one pot domino process will be realized. Here, interesting to note that the synthesis of various polyhydropyridines could be achieved from common starting materials by just tuning the reaction conditions. Although the use of preformed imines was an option, the whole process will be greener and more economical if we start with aromatic aldehydes and add other substrates and reagents in same pot sequentially. This reaction could conveniently follow multi-component

pathway through in situ formation of imine (step 1), Proline-catalytic Mannich reaction-cyclization (step 2), in situ site-selective oxidation with IBX (step 3) and finally selective reduction (step 4) as one pot domino-approach to furnish 1,2,5,6-THPs **20** with high stereoselectivity without any isolation at intermediate stage as shown in (**Scheme 4.6**). By keeping this idea in mind and the previous experience in this direction, we quickly established the reaction conditions by taking *p*-nitrobenzaldehyde **16c** as model aromatic aldehyde along with *p*-anisidine **17** and glutaraldehyde **18** as shown in **Table 4.1**.



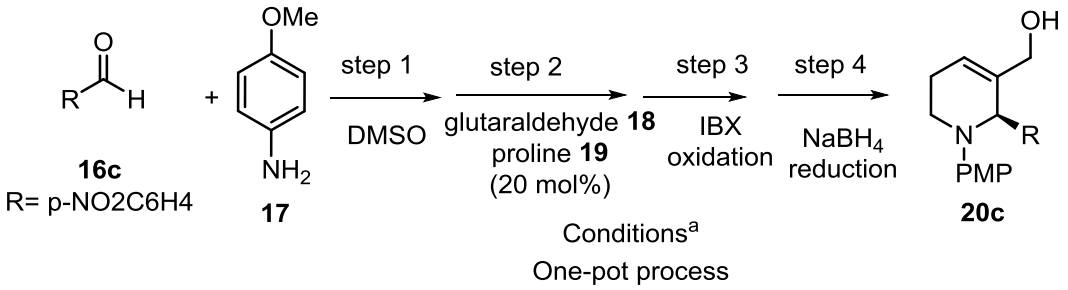
Scheme 4.6 Organocatalytic asymmetric synthesis of 1,2,5,6-THPs

4.2 Results and discussion:

During our experimental studies, we initially carried out all steps of the multi-component/domino-reaction at room temperature with proline **19** (20 mol%) in DMSO as preferred solvent. Interestingly, this amine catalyzed direct Mannich reaction/cyclization between glutaraldehyde **18** (25% sol.) and *in situ* generated imine, followed by site selective IBX-oxidation and acid me reduction as one-pot domino sequence gave product 1,2,5,6-THP **20c** exclusively in moderate yield (65%) and good enantiomeric ratio (88:12) (entry 1, **Table 4.1**). We did not alter the amine catalyst or solvent as they turn out to be best in our previous studies. However, by changing the reaction temperature at individual steps, we could obtain our product

with 80% yield and excellent 97:3 er (entry 2, **Table 4.1**). A furtherchange in the reaction conditions (entry 3, **Table 4.1**), and catalyst loading (entry 4, **Table 4.1**), resulted in a reduction of the overall yield. Thus, we choose to perform this one pot protocol of sequential multi-component amine catalyzed [4+2] annulation/IBX oxidation/acid mediated $NaBH_4$ reduction through preferred conditions (entry 2, **Table 4.1**).

Table 4.1 Optimization of the reaction conditions (**20c**)



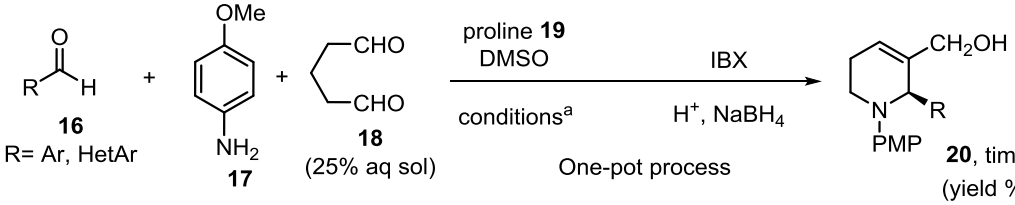
Entry	step 1	step 2	step 3	step 4	Yield (%)[b]	er[c]
1	rt, 3 h	rt, 5 h	IBX, rt, 5 h	H^+, $NaBH_4$, rt, 3 h	65	88:12
2	rt, 3 h	10 °C, 6 h	IBX, 40 °C, 4 h	H^+, $NaBH_4$, 0 °C-rt, 3 h	80	97:3
3[d]	rt, 3 h	10 °C, 6 h	IBX, 40 °C, 4 h	$NaBH_4$, 0 °C-rt, 3 h	49	97:3
4[e]	rt, 3 h	10 °C, 12 h	IBX, 40 °C, 4 h	H^+, $NaBH_4$, 0 °C-rt, 3 h	53	97:3

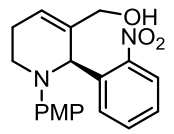
[a]Unless otherwise indicated, the reaction was carried out with: (step 1) **16c** (0.3 mmol), **17** (0.3 mmol), DMSO (3.0 mL), (step 2) glutaraldehyde **18** (25% aqueous sol., 0.9 mmol), L-Proline **19** (20 mol %), (step 3) IBX (120 mol %), and (step 4) MeOH (3.0 mL), $NaBH_4$ (excess), CH_3CO_2H (200 mol %). [b]Isolated yield of **20c** refer to **16c**. [c]Determined using stationary chiral columns. [d]CH_3CO_2H (200 mol %), and MeOH (3.0 mL) were not added during step 4. [e]Catalyst**19** (10 mol %).

Once we established the reaction conditions for this one pot domino sequence, we turn our attention to check the substrate scope with respect to a variety of aromatic aldehydes **2** having various substituents. This one pot protocol advance well in almost all cases when aromatic aldehydes **2** were decorated with electron withdrawing groups (EWG) (e.g. $-NO_2$, −F, −Cl, −Br and –CN) at the ortho-, meta-, or para- positions, and furnished the corresponding 1,2,5,6-DHPs **20a**-**20p** (**Table 4.2**) with good yields and high enantiomeric ratio's. In all the cases, aromatic

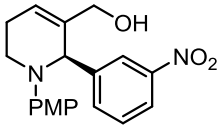
aldehyde **16** was stirred with *p*-anisidine **17** at rt for about 3 h (step 1) for *in situ* generation of imine, which subsequently used for further steps. The amine catalyzed Mannich reaction-cyclization (step 2) was rather slow in case of imines generated from aldehydes substituted at *ortho*-position.

Table 4.2 Substrate scope of the developed method for (**20**)

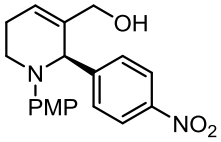




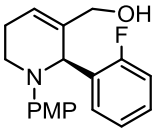
20a, 10 h, 63%
er = 97:3



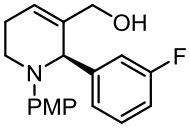
20b, 8 h, 74%
er = 94:6



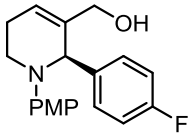
20c, 6 h, 80%
er = 97:3



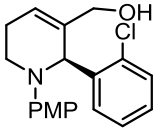
20d, 9 h 61%
er = 98:2



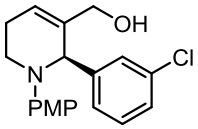
20e, 7 h, 66%
er = 81:19



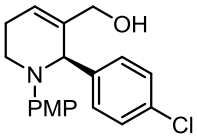
20f, 7 h, 68%
er = 83:17



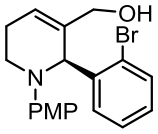
20g, 10 h, 65%
er = 97:3



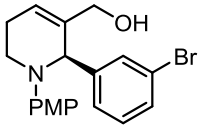
20h, 8 h, 68%
er = 85:15



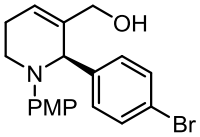
20i, 8 h, 70%
er = 86:14



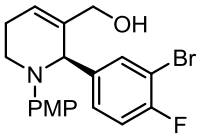
20j, 10 h, 58%
er = 98:2



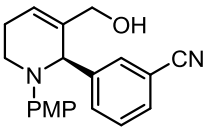
20k, 9 h, 67%
er = 90:10



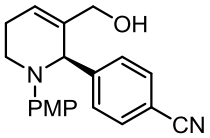
20l, 9 h, 69%
er = 92:8



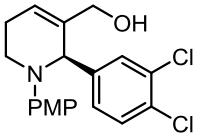
20m, 8 h, 71%
er = 87:13



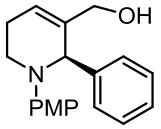
20n, 9 h, 74%
er = 88:12



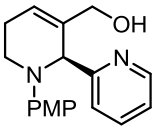
20o, 9 h, 78%
er = 90:10



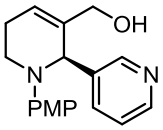
20p, 9 h, 70%
er = 93:7



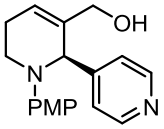
20q, 10 h, 58%
er = 85:15



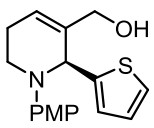
20r, 10 h, 63%
er = 91:9



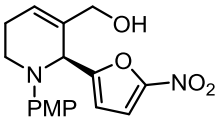
20s, 11 h, 72%
er = 81:19



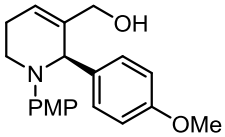
20t, 10 h, 76%
er = 96:4



20u, 10 h, 53%
er = 86:14



20v, 8 h, 63%
er = 86:14



20w, 24 h, nr

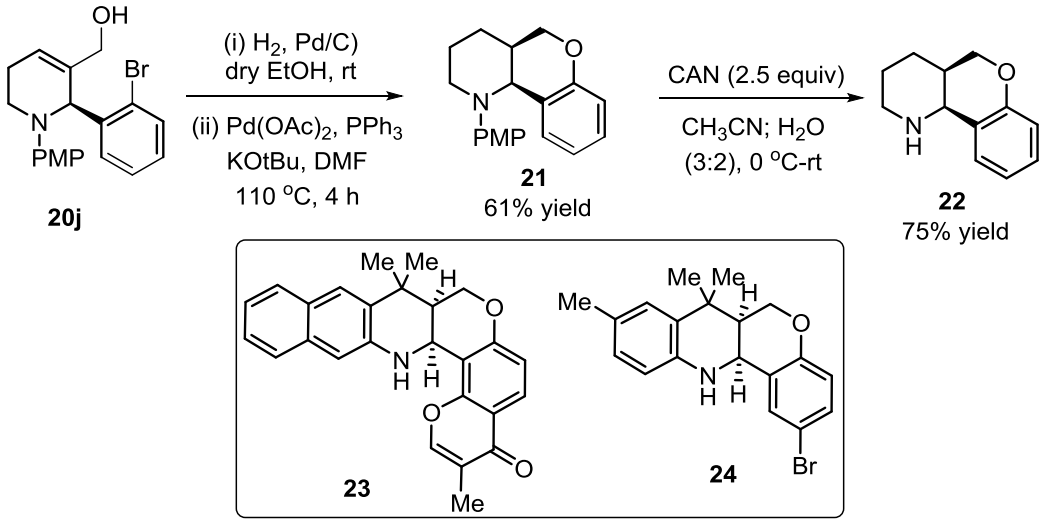
[a]Unless otherwise indicated, the reaction was carried out with (***step 1***) **16**(0.3 mmol), **17** (0.3 mmol), DMSO (3.0 mL), 3 h, (***step 2***) glutaraldehyde **18** (25% aqueous sol., 0.9 mmol), L-

Proline **19** (20 mol %), [b]time required (h), (***step 3***) IBX (120 mol %), and (***step 4***) $NaBH_4$ (excess), MeOH (3.0 mL), CH_3CO_2H (200 mol %) in single flask. [c]isolated yield of **20** refer to **6**. (≤10% of corresponding Ar/HetAr-CH_2OH was obtained in all the cases). [d]Determined using stationary chiral columns.

A similar result was obtained as 1,2,5,6-THP **20t** (**Table 4.2**) when benzaldehyde **16t** was used for this one-pot sequence. Pleasantly, compound **20r**-**20v** (**Table 4.2**) were also obtained in good yields and high enantiomeric ratio, when hetero-aromatic aldehydes were employed under standardized conditions. This reaction failed to give desired product **20w** (**Table 4.2**) when electronically rich aryl-aldehyde was employed.

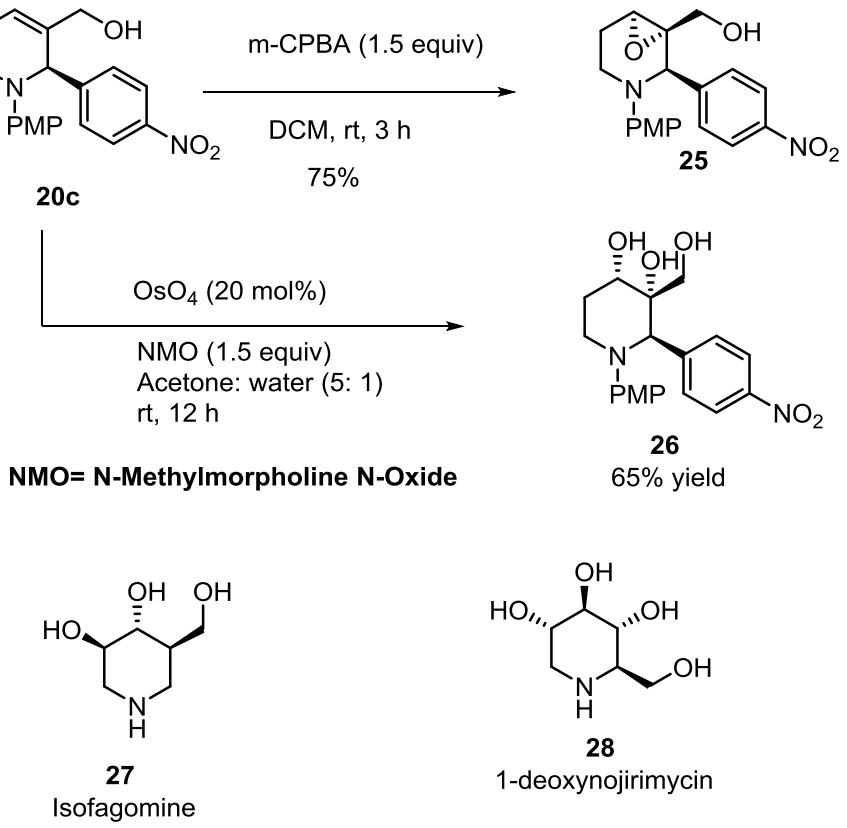
4.3 Synthetic application of the developed method:

The product 1,2,5,6-THPs of this one-pot sequence, carrying a double bond and alcohol functionality as well as some functional group at the aromatic ring, are interesting scaffolds for further functionalization. Therefore, to demonstrate the synthetic potential of these compounds, we initially developed a quick synthesis of piperidine-fused-chroman **22** from compound **20j**. As shown in **Scheme 4.7**, Pd/C reduction of **20j** followed by metal catalyzed intramolecular C-O coupling resulted compound **21**, which subsequently gave hexahydrochromeno[4,3-*b*]pyridine **22** after PMP-cleavage under mild condition. The polycyclic compound **22** and similar skeletons are present in many interesting bioactive compounds, like- **23** and **24**.[80-84]



Scheme 4.7 Rapid synthesis of hexahydrochromeno[4,3-*b*]pyridine

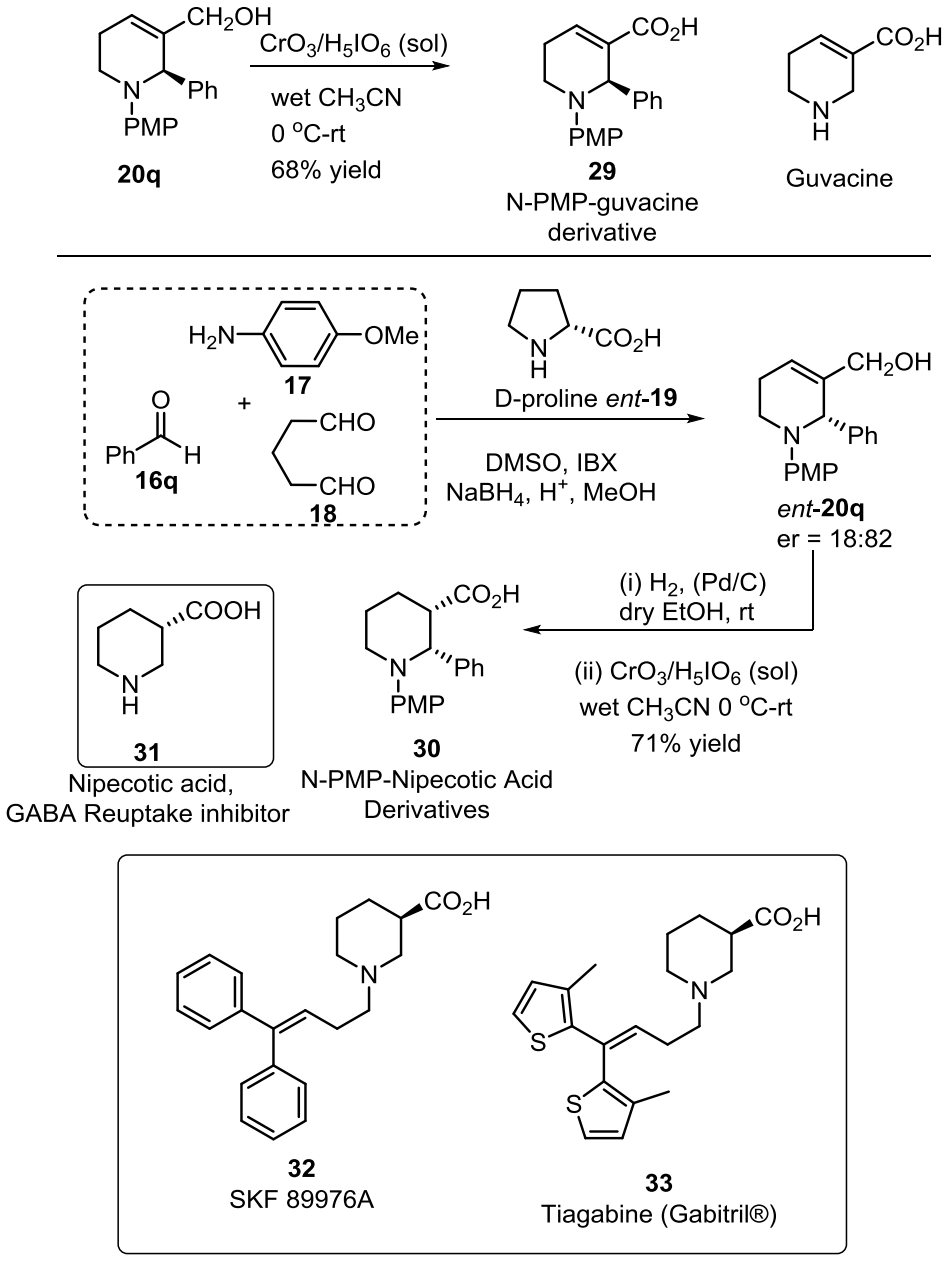
Next, we decide to derivatize the alkene-bond of the ring through diastereoselective epoxidation and dihydroxylation reaction. Compound **20c** was easily converted to corresponding epoxidated **25**, and dihydroxylated compound **26**, under standardized conditions with good yields respectively (**Scheme 4.8**). The similar polyhydroxyl-piperidines are important compounds under the category of iminosugars as glycosidase inhibitors. [85]



Scheme 4.8 Synthesis of important polyfunctionalized piperidines

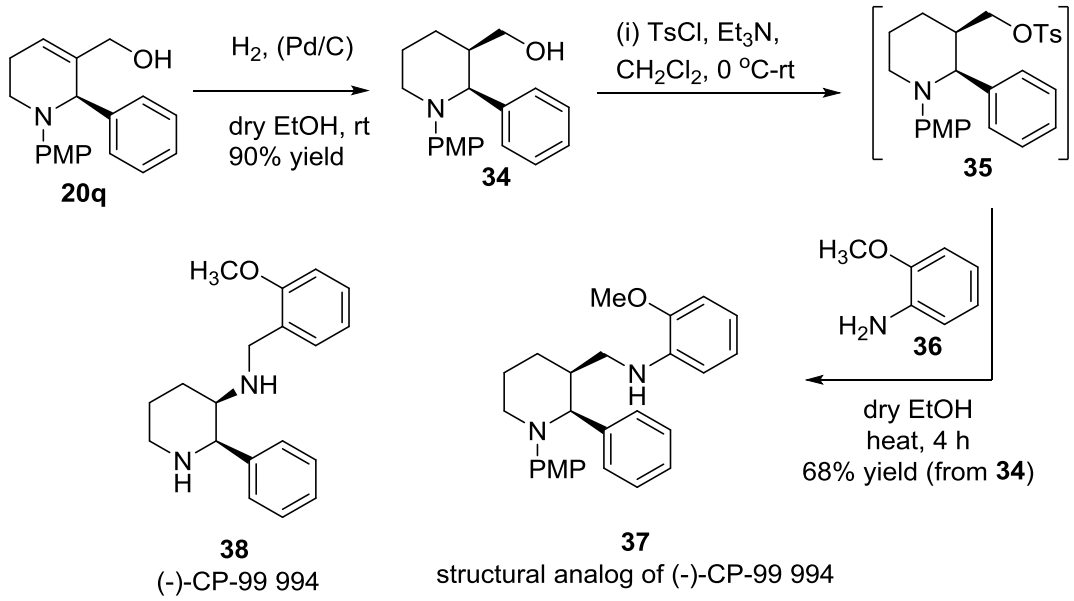
Interestingly, direct oxidation of primary alcohol functionality of **20c** to corresponding carboxylic acid provides a rapid access to guvacine derivatives **29** (**Scheme 4.9**). Further, we also showed the synthetic utility of our approach to synthesize *ent*-**20m** opposite enantiomer of compound **20** by just changing the catalyst from L- to D-proline under standardized conditions with similar yields and enantiomeric ratio. The resulting product *ent*-**20m** was next used for the synthesis of nipecotic acid derivative **30** with 71% yield (after two steps) through reduction-oxidation sequence as shown in **Scheme 4.9.** Nipecotic acid **31**, a cyclic amino acid and considered as a conformationally restricted β-alanine analog, shows high in vitro activity as an

inhibitor of [^{3}H] GABA uptake.[86-89] Nipecotic acid derivatives with a lipophilic side chain, such as SKF 89976A, **32** shows a significantly increased potency compared to their parent amino acid **31**, whereas another derivative Tiagabine (Gabitril®, **33**), used as a drug in add-on therapy of epilepsy.[90,91] Fast access to both enantiomers of nipecotic acid derivatives through this approach is worthy to note as the production of enantiomerically pure nipecotic acid ($ 113.70/g, Aldrich) is 2000 times more expensive than its pyridine analogue, nicotinic acid.



Scheme 4.9 Efficient synthesis of guvacine and nipecotic acid derivatives

The application of this strategy was further showed to synthesize structural analogue **37** of (–)-CP 99 994, as this compound **38** carries interesting biological activity. [92-96] In this context, firstly Pd/C catalyzed hydrogenation of THP-compound **20q** gave *syn*-2,3-substituted-piperidine **34** in 90% yield. The alcoholic group was converted into –OTs under standard condition, the crude **35** was further subjected to nucleophillic substitution with 2-methoxyaniline **36** under heating condition resulted in compound **37** (68% yield from **34, Scheme 4.10**).



Scheme 4.10 Synthesis of structural analogue of **38**

4.4 Conclusion:

In summary of this chapter, we have developed an efficient multicomponent-domino sequence in a single flask for the asymmetric synthesis of functionalized 1,2,5,6-tetrahydropyridines (THPs) **20**. This method proceeded through amine catalyzed Mannich reaction-cyclization of in situ generated imine and glutaraldehyde followed by domino selective IBX-oxidation/$NaBH_4$-reduction under a mild reaction condition, without isolation of intermediate compounds. Further applications of developed method were also shown for: (*i*) quick synthesis of hexahydrochromeno[4,3-*b*]pyridine (*ii*) synthesis of polyhydroxy-piperidine (*iii*) synthesis of guvacine and nipecotic acid derivative (*iv*) synthesis of a structural analogue of (–)-CP 99 994, as medicinally important scaffolds. Therefore, the present methodology has potential relevance in the preparation of other medicinally important compounds related to those described here.

4.5 General Experimental Methods:

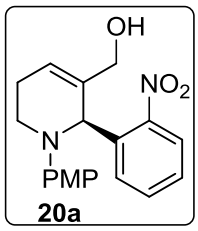
All reactions under standard conditions were monitored by thin-layer chromatography (TLC) through SiO_2 gel F-254 plates. All reagents were of analytical grade and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution and spectral data were reported in ppm relative to tetramethylsilane (TMS) as internal standard. High resolution mass spectra were recorded using quadruple electro spray ionization (ESI) technique. HPLC was performed on Water-2998-instrument with CHIRALPAK-IA and IB columns using hexane/2-propanol.

4.6 General procedure for THPs 20:

To a stirred solution of aryl aldehyde **16** (0.3 mmol) in DMSO (3.0 mL) at rt was added *p*-anisidine **17** (0.3 mmol) and stirred for additional 3 hrs at same temperature. To this mixture, was added glutaraldehyde **18** (25 % sol. in water, 0.360 mL, 0.9 mmol), and L-proline **19** (6.9 mg, 0.06 mmol) and taken to 10 °C. This reaction mixture was further stirred at the same temperature until the in situ generated imine was consumed completely as monitored by TLC. IBX (2-Iodoxybenzoic acid) (1.2 equiv, 0.36 mmol) was added into the same flask and further heated to 40 °C for 4 hrs. This reaction mixture was then cooled to 0 °C and Methanol (3.0 mL) was added followed by $NaBH_4$ (in excess and portion wise) along with CH_3CO_2H (200 mol %) until the dark red color of the solution turned into pale reddish yellow. Reaction was quenched slowly with saturated $NaHCO_3$ (5.0 mL, 20% sol.) and stirred with ethyl acetate (10 mL) for 10 min at rt and organic layer was separated out. The aqueous layer was further extracted with ethyl acetate (10 mL) and the combined organic extracts were washed with brine solution, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure after filtration. Purification was performed by a silica gel column and eluted with hexane/EtOAc to give product **20** (58-80% yields). The enantiomeric ratios (er) of the products were determined by stationary chiral phase HPLC analysis.

4.7 Characterization data:

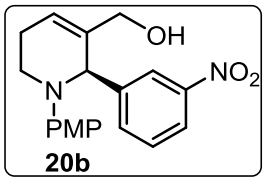
(*R*)-(1-(4-methoxyphenyl)-2-(2-nitrophenyl)-1,2,5,6-tetrahydropyridin-3- yl)methanol(20a)



20a

Yellow viscous oil, (64 mg, 63% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77–1.79 (bs, 1H), 2.18–2.23 (m, 1H), 2.25-2.32 (m, 1H), 3.00–3.07 (m, 1H), 3.15–3.19 (m, 1H), 3.73 (s, 3H), 4.06 (s, 2H), 5.80 (s, 1H), 6.16 (t, *J* = 4.2 Hz, 1H), 6.72 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 7.32–7.36 (m, 1H), 7.50–7.51 (m, 2H), 7.63 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.70, 44.50, 55.35, 55.57, 64.91, 114.20 (2C), 121.40 (2C), 124.16, 125.61, 128.02, 130.13, 131.66, 135.19, 136.73, 143.78, 150.57, 154.65; IR (KBr)/cm^{-1} 3448, 2924, 2854,1520,1466, 1350, 1242, 1180, 1034; HRMS (ESI): Calcd for $C_{19}H_{20}N_2O_4$ (MH^+) 341.1501; Found: 341.1504. $[\alpha]_D^{25}$ = – 81.4 (*c* 0.1, CH_2Cl_2). HPLC analysis: 97:3 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 94/06), flow rate (0.8 mL/min), t_R (minor) = 15.224 min, t_R (major) = 22.808 min].

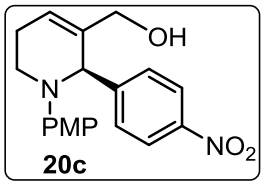
(*R*)-(1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20b)



20b

Pale yellow viscous liquid, (75 mg, 74% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33–2.47 (m, 2H), 3.10–3.22 (m, 2H), 3.73 (s, 3H), 3.86 (d, *J* = 12.8 Hz, 1H), 4.01 (d, *J* = 12.8 Hz, 1H), 5.20 (s, 1H), 6.16 (t, *J* = 3.1 Hz,1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.85 (d, *J* = 9.0 Hz, 2H), 7.37 (t, *J* = 7.9 Hz, 1H), 7.45 (d, *J* = 7.9 Hz, 1H), 8.02–8.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.68, 43.00, 55.40, 61.64, 64.78, 114.24 (2C), 121.24 (2C), 122.41, 123.23, 125.30, 128.76, 135.14, 136.77, 141.61, 143.76, 147.90, 154.34; IR (KBr)/cm^{-1} 3418, 2924, 2847, 1605, 1520, 1458, 1342, 1250, 1188, 1034; HRMS (ESI): Calcd for $C_{19}H_{20}N_2O_4$ (MH^+) 341.1501; Found: 341.1508. $[\alpha]_D^{25}$ = –173 (*c* 0.5, CH_2Cl_2). HPLC analysis: 94:6 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 29.538 min, t_R (major) = 33.207 min].

(*R*)-(1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20c):

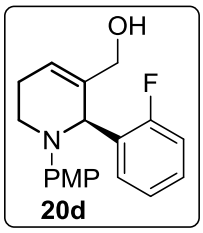


20c

Yellowish viscous oil, (82 mg, 80% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32–2.47 (m, 2H), 3.11–3.22 (m, 2H), 3.74 (s, 3H), 3.85 (d, *J* = 12.7 Hz, 1H), 3.99 (d, *J* = 12.8 Hz, 1H), 5.18 (s, 1H), 6.14 (t, *J* = 3.2 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 2H), 8.07 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.79, 42.96, 55.32, 61.74, 66.59, 114.15 (2C), 121.20 (2C),

122.98 (2C), 124.84, 129.48 (2C), 136.81, 143.68, 146.82, 147.80, 154.28; IR (KBr)/cm^{-1} 3446, 2925, 2854,1522, 1468, 1350, 1241, 1180, 1034; HRMS (ESI Calcd for $C_{19}H_{20}N_2O_4$ (MH^+) 341.1501; Found: 341.1495. $[\alpha]_D^{25}$= –198(*c* 1.0, CH_2Cl_2). HPLC analysis: 97:3er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 80/20), flow rate (1.0 mL/min), t_R (minor) = 17.932 min, t_R (major) = 22.037 min].

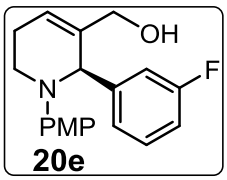
(*S*)-(2-(2-fluorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20d)



20d

Reddish viscous oil, (57 mg, 61% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17–2.22 (m, 1H), 2.27–2.32 (m, 1H), 3.28–3.31 (m, 2H), 3.74 (s, 3H), 3.94 (s, 2H), 5.48 (s, 1H), 6.11 (t, *J* = 3.9 Hz, 1H), 6.77 (d, *J* = 8.9 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.17–7.22 (m, 2H), 7.32–7.34 (m, 1H) 7.39–7.41(m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.38, 44.79, 55.37, 57.34, 64.71, 114.08 (2C), 120.67 (2C), 124.84, 126.43, 128.51, 129.81, 129.96, 135.32, 137.64, 138.39, 144.27, 153.89; IR (KBr)/cm^{-1} 3140, 2916, 2850,1660, 1508, 1246, 1178; HRMS (ESI): Calcd for $C_{19}H_{20}FNO_2$ (MH^+) 314.1556; Found: 314.1559. $[\alpha]_D^{25}$ = –46.1 (*c* 0.8, CH_2Cl_2). HPLC analysis: 98:2er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 11.835 min, t_R (major) = 14.871 min].

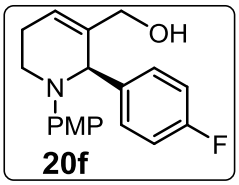
(*R*)-(2-(3-fluorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20e)



20e

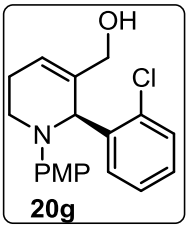
Yellow viscous liquid, (62 mg, 66% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26–2.31 (m, 1H), 2.39–2.47 (m, 1H), 3.18–3.21 (m, 2H), 3.74 (s, 3H), 3.91 (d, *J* = 12.4 Hz, 1H), 3.99 (d, *J* = 12.7 Hz, 1H), 5.08 (s, 1H), 6.10 (t, *J* = 4.3 Hz, 1H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.2 Hz, 3H), 6.90–6.92 (m, 2H), 7.14–7.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ24.62, 42.63, 55.44, 61.87, 64.97, 114.15 (2C), 114.33, 115.41, 115.62, 120.88 (2C), 124.39, 124.67, 129.27, 129.35, 137.59, 144.24, 153.99; IR (KBr)/cm^{-1} 3420, 2924, 2848, 1655, 1589, 1247, 1170; HRMS (ESI Calcd for $C_{19}H_{20}FNO_2$ (MH^+) 314.1556; Found: 314.1562. $[\alpha]_D^{25}$ = –41.3 (*c* 0.6, CH_2Cl_2). HPLC analysis: 81:19er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 17.480 min, t_R (major) = 20.078 min].

(*R*)-(2-(4-fluorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol(20f)



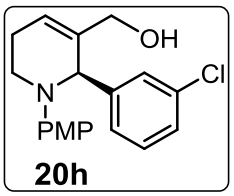
Yellowish viscous liquid, (64 mg, 68% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25–2.26 (m, 1H), 2.39–2.47 (m, 1H), 3.14–3.17 (m, 2H), 3.74 (s, 3H), 3.93 (m, 2H), 5.07 (s, 1H), 6.09 (t, *J* = 4.4 Hz, 1H), 6.75 (d, *J* = 9.2 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 6.89 (t, *J* = 8.7 Hz, 2H), 7.07 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.76, 42.35, 55.43, 61.80, 65.02, 114.10 (2C), 114.62, 114.83, 121.16 (2C), 124.14, 130.35, 130.43, 134.74, 137.93, 144.31, 154.04, 160.83; IR (KBr)/cm^{-1} 3426, 2924, 2854, 1643, 1597, 1512, 1242, 1034, 825, 725; HRMS (ESI): Calcd for $C_{19}H_{20}FNO_2$ (MH^+) 314.1556; Found: 314.1549. $[\alpha]_D^{25}$ = –101 (*c* 0.2, CH_2Cl_2). HPLC analysis: 83:17er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 18.826 min, t_R (major) = 20.510 min].

(*S*)-(2-(2-chlorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20g)



Dark red viscous liquid,(64 mg, 65% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16–2.23 (m, 1H), 2.25–2.34 (m, 1H), 3.28–3.31 (m, 2H), 3.74 (s, 3H), 3.93 (s, 2H), 5.48 (s, 1H), 6.11 (t, *J* = 3.8 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 7.15–7.22 (m, 2H), 7.32–7.34 (m, 1H), 7.37–7.41 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.35, 44.76, 55.38, 57.30, 64.75, 114.07 (C), 120.64 (2C), 124.90, 126.44, 128.53, 129.83, 129.96, 153.33, 137.62, 138.38, 144.25, 153.87; IR (KBr)/cm^{-1} 3418, 2924, 2862, 1659, 1512, 1458, 1250, 1188, 1095, 1034; HRMS (ESI): Calcd for $C_{19}H_{20}ClNO_2$ (MH^+) 330.1261; Found : 330.1255. $[\alpha]_D^{25}$ = –76.6 (*c* 0.3, CH_2Cl_2,). HPLC analysis: 97:3 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 90/10), flow rate (0.6 mL/min), t_R (minor) = 8.278 min, t_R (major) = 11.601 min].

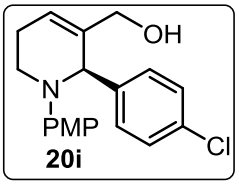
(*R*)-(2-(3-chlorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol(20h)



Pale yellow liquid,(67 mg, 68% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (bs, 1H), 2.25–2.30 (m, 1H), 2.40–2.46 (m, 1H), 3.17–3.20 (m, 2H), 3.78 (s, 3H), 3. 89 (d,*J* = 12.8 Hz, 1H), 3.98 (d, *J* = 12.8 Hz, 1H), 5.06 (s, 1H), 6.09 (t, *J* = 3.2 Hz, 1H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 6.98–7.01 (m, 1H), 7.08–7.13 (m, 1H), 7.15–7.19 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.47, 42.47, 55.42, 6180, 64.76, 114.14 (2C), 120.87 (2C), 124.36, 127.25, 127.46, 128.64, 129.12, 133.79,

137.33, 141.36, 144.03, 154.01; IR (KBr)/cm^{-1} 3464, 2924, 2947, 1643, 1512, 1242, 1188, 1088, 1034; HRMS (ESI): Calcd for $C_{19}H_{20}ClNO_2$ (MH^+) 330.1261; Found : 330.1267. $[\alpha]_D^{25}$ = –97.6 (*c* 0.8, CH_2Cl_2).HPLC analysis: 85:15 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 17.376 min, t_R (major) = 19.863 min].

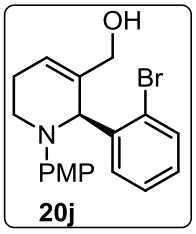
(*R*)-(2-(4-chlorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20i)



20i

Colorless viscous liquid,(69 mg, 70% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25–2.30 (m, 1H), 2.38–2.46 (m, 1H), 3.12–3.17 (m, 2H), 3.74 (s, 3H), 3.87 (d, *J* = 13.1 Hz, 1H), 3.95 (d, *J* = 12.8 Hz, 1H), 5.06 (s, 1H), 6.08 (t, *J* = 3.2 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.1 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.71, 42.31, 55.38, 61.76, 64.78, 114.08 (2C), 121.09 (2C), 124.11, 127.99 (2C), 130.16 (2C), 133.02, 137.42, 137.60, 144.12, 154.02; IR (KBr)/cm^{-1} 3418, 2916, 2847, 1651, 1597, 1594, 1242, 1188, 1095, 1026; HRMS (ESI): Calcd for $C_{19}H_{20}ClNO_2$ (MH^+) 330.1261; Found : 330.1263. $[\alpha]_D^{25}$ = – 143.2 (*c* 0.7, CH_2Cl_2). HPLC analysis: 86:14 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 20.054 min, t_R (major) = 23.154 min].

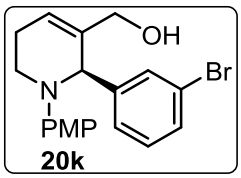
(*S*)-(2-(2-bromophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20j)



20j

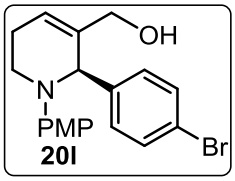
Reddish viscous liquid,(65 mg, 58% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ2.30–2.35 (m, 2H), 3.14–3.19 (m, 1H), 3.23–3.30 (m, 2H), 3.52 (d, *J* = 13.9 Hz, 1H), 3.60 (d, *J* = 14.0 Hz, 1H), 3.76 (s, 3H), 5.55 (s, 1H), 5.91 (bs, 1H), 6.82 (d, *J* = 9.2 Hz, 2H), 6.90 (d, *J* = 9.1 Hz, 2H), 7.14–7.18 (m, 1H), 7.33–7.39 (m, 1H), 7.53–7.55 (m, 1H), 7.59–7.61 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.36, 45.13, 55.36, 59.75, 64.72, 114.04 (2C), 121.06 (2C), 124.97, 126.17, 127.03, 128.78, 130.19, 133.18, 137.67, 140.09, 144.35, 153.98; IR (KBr)/cm^{-1} 3317, 3055, 2916, 2847, 1512, 1450, 1242, 1180, 1034; HRMS (ESI): Calcd for $C_{19}H_{20}BrNO_2$(MH^+) 374.0755; Found: 374.0759. $[\alpha]_D^{25}$ = –32.3 (*c* 0.6, CH_2Cl_2). HPLC analysis: 98:2 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 10.465 min, t_R (major) = 13.302 min].

(*R*)-(2-(3-bromophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol(20k)



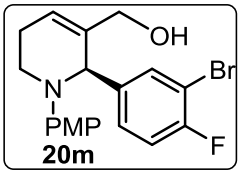
Yellow viscous liquid, (75 mg, 67% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27–2.28 (m, 1H), 2.41–2.48 (m, 1H), 3.19–3.22 (m, 2H), 3.77 (s, 3H), 3.92 (d, *J* = 12.9 Hz, 1H), 4.01 (d, *J* = 12.8 Hz, 1H), 5.07 (s, 1H), 6.12 (t, *J* = 4.2 Hz, 1H), 6.79 (d, *J* = 9.2 Hz, 2H), 6.88 (d, *J* = 9.1 Hz, 2H), 7.05–7.12 (m, 2H), 7.34–7.37 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.44, 42.35, 55.40, 61.75, 64.69, 114.12 (2C), 120.86 (2C), 122.09, 124.34, 127.66, 129.40, 130.34, 131.49, 137.24, 141.57, 144.01, 153.98; IR (KBr)/cm^{-1} 3302, 3055, 2916, 2839, 1566, 1512, 1458, 1242, 1180, 1034; HRMS (ESI): Calcd for $C_{19}H_{20}BrNO_2$ (MH^+) 374.0755; Found: 374.0762. $[\alpha]_D^{25}$ = –113.3 (*c* 1.5, CH_2Cl_2). HPLC analysis: 90:10 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 17.692 min, t_R (major) = 19.870 min].

(*R*)-(2-(4-bromophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20l)



Colorless viscous liquid,(77 mg, 69% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25–2.30 (m, 1H), 2.38–2.46 (m, 1H), 3.13–3.16 (m, 2H), 3.74 (s, 3H), 3.87 (d, *J* = 12.0 Hz, 1H), 3.96 (d, *J* = 12.9 Hz, 1H), 5.04 (s, 1H), 6.08 (t, *J* = 4.2 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.99 (d, *J* = 9.6 Hz, 2H), 7.33 (d, *J* = 9.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.70, 42.31, 55.37, 61.79, 64.70, 114.09 (2C), 121.05 (2C), 121.24, 124.07, 130.51 (2C), 130.91 (2C), 137.52, 137.94, 144.08, 154.01; IR (KBr)/cm^{-1} 3418, 2916, 2908, 1659, 1504, 1242, 1188, 1026, 818; HRMS (ESI): Calcd for $C_{19}H_{20}BrNO_2$ (MH^+) 374.0755; Found: 374.0757. $[\alpha]_D^{25}$ = – 187.5 (*c* 0.8, CH_2Cl_2). HPLC analysis: 92:8 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 21.191 min, t_R (major) = 25.148 min].

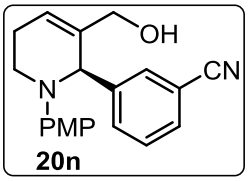
(*R*)-(2-(3-bromo-4-fluorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20m):



Pale yellow viscous liquid, (83 mg, 71% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26–2.31 (m, 1H), 2.37–2.45 (m, 1H), 3.09–3.17 (m, 2H), 3.75 (s, 3H), 3.86–3.89 (d, *J* = 12.3 Hz, 1H), 3.98 (d, *J* = 12.9 Hz, 1H), 5.04 (s, 1H), 6.10 (t, *J* = 3.0 Hz, 1H), 6.77 (d, *J* = 9.1 Hz, 2H), 6.84 (d, *J* = 9.2 Hz, 2H), 6.92–6.96 (m, 1H), 6.98–7.02 (m, 1H), 7.32–7.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.56, 42.35, 55.40, 61.31,

64.64, 114.16 (2C), 121.18 (2C), 124.50, 129.45, 129.52, 133.41, 136.46, 137.22, 143.84, 154.21, 156.91, 159.36; IR (KBr)/cm^{-1} 3279, 3047, 2914, 2847, 1558, 1504, 1242, 1180, 1034; HRMS (ESI): Calcd for $C_{19}H_{19}BrFNO_2$ (MH^+) 392.0661; Found: 392.0667. $[\alpha]_D^{25}$ = – 95.4 (*c* 1.2, CH_2Cl_2). HPLC analysis: 87:13 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 17.880 min, t_R (major) = 20.715 min].

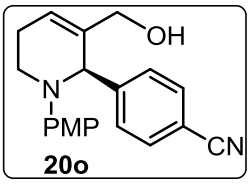
(*R*)-3-(3-(hydroxymethyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-2-yl)benzonitrile (20n)



20n

Yellow viscous liquid, (71 mg, 74% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29–2.38 (m, 1H), 2.40–2.45 (m, 1H), 3.07–3.21 (m, 2H), 3.74 (s, 3H), 3.82–3.85 (m, 1H), 3.98 (d, *J* = 13.0 Hz, 1H), 5.11 (s, 1H), 6.13 (t, *J* = 3.1 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 7.28–7.32 (m, 1H), 7.34–7.37 (m, 1H), 7.47–7.50 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.55, 42.70, 55.33, 61.53, 64.50, 111.65, 114.15 (2C), 118.85 121.11 (2C), 124.84, 128.62, 130.92, 132.02, 133.46, 136.75, 140.74, 143.70, 154.20; IR (KBr)/cm^{-1} 3418, 2924, 2947, 2230, 1605, 1512, 1458, 1242, 1188, 1034; HRMS (ESI): Calcd for $C_{20}H_{20}N_2O_2$ (MH^+) 321.1603; Found: 321.1609. $[\alpha]_D^{25}$ = –143.3 (*c* 0.8, CH_2Cl_2). HPLC analysis: 88:12 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 85/15), flow rate (0.5 mL/min), t_R (major) = 16.913 min, t_R (minor) = 21.912 min].

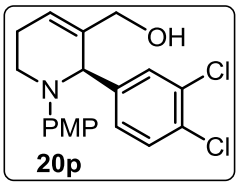
(*R*)-4-(3-(hydroxymethyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-2-yl)benzonitrile (20o)



20o

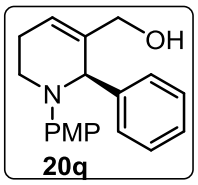
Pale yellow viscous liquid, (74 mg, 78% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28–2.34 (m, 1H), 2.38–2.47 (m, 1H), 3.08–3.17 (m, 2H), 3.74 (s, 3H), 3.84 (d, *J* = 12.3 Hz, 1H), 3.97 (d, *J* = 12.9 Hz, 1H), 5.12 (s, 1H), 6.12 (t, *J* = 3.1 Hz, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.82 (d, *J* = 9.1 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.50 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.62, 42.77, 55.28, 61.88, 64.42, 110.77, 114.09 (2C), 118.70, 121.02 (2C), 124.58, 129.36 (2C), 131.55 (2C), 136.78, 143.73, 144.74, 154.13; IR (KBr)/cm^{-1} 3418, 2924, 2862, 2230, 1659, 1512, 1458, 1250, 1188, 1095, 1034; HRMS (ESI): Calcd for $C_{20}H_{20}N_2O_2$ (MH^+) 321.1603; Found: 321.1605. $[\alpha]_D^{25}$ = – 182.4 (*c* 1.5, CH_2Cl_2). HPLC analysis: 90:10 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 80/20), flow rate (0.5 mL/min), t_R (minor) = 16.974 min, t_R (major) = 18.771 min].

(*R*)-(2-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20p)



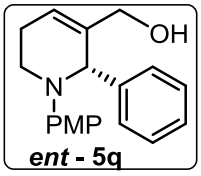
Orange liquid, (76 mg, 70% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25–2.30 (m, 1H), 2.36–2.44 (m, 1H), 3.08–3.17 (m, 2H), 3.73 (s, 3H), 3.85 (d, *J* = 12.3 Hz,1H), 3.97 (d, *J* = 12.9 Hz, 1H), 5.03 (s, 1H), 6.09 (t, *J* = 3.1 Hz, 1H),6.75 (d, *J* = 9.1 Hz, 2H), 6.83 (d, *J* = 9.1 Hz, 2H), 6.93 (dd, *J* = 8.2 Hz, *J* = 2.0 Hz, 1H), 7.23–7.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.56, 42.53, 55.36, 61.33, 61.51, 114.19 (2C), 121.04 (2C), 124.49, 128.29, 129.70, 130.39, 131.13, 131.86, 137.03, 139.51, 143.81, 154.18; IR (KBr)/cm^{-1} 3410, 3055, 2916, 2839, 1605, 1512, 1458, 1396, 1242, 1188, 1034; HRMS (ESI): Calcd for $C_{19}H_{19}Cl_2NO_2$ (MH^+) 364.0871; Found: 364.0876. $[\alpha]_D^{25}$ = – 193 (*c* 1.3, CH_2Cl_2). HPLC analysis: 93:7 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 17.848 min, t_R (major) = 21.804 min].

(*R*)-(1-(4-methoxyphenyl)-2-phenyl-1,2,5,6-tetrahydropyridin-3-yl)methanol (20q)



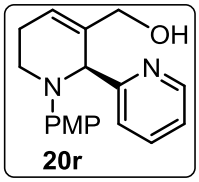
Yellow viscous oil, (51 mg, 58% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23–2.28 (m, 1H), 2.40–2.45 (m, 1H), 3.17–3.21 (m, 2H), 3.73 (s, 3H), 3.93 (m, 2H), 5.09 (s, 1H), 6.07 (bs, 1H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.86 (d, *J* = 9.1 Hz, 2H), 7.12–7.15 (m, 2H), 7.20–7.22 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.54, 42.22, 55.39, 62.31, 64.94, 114.03 (2C), 120.73 (2C), 123.79, 127.27, 127.88 (2C), 128.87 (2C), 137.95, 139.10, 144.41, 153.73; IR (KBr)/cm^{-1} 3394, 2924, 2854, 1736, 1512, 1458, 1381, 1242, 1180, 1034, 875; HRMS (ESI): Calcd for $C_{19}H_{21}NO_2$ (MH^+) 296.1650; Found: 296.1658. $[\alpha]_D^{25}$ = –140.5 (*c* 0.5, CH_2Cl_2). HPLC analysis: 85:15 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 88/12), flow rate (0.5 mL/min), t_R (minor) = 13.505 min, t_R (major) = 15.262 min].

(*S*)-(1-(4-methoxyphenyl)-2-phenyl-1,2,5,6-tetrahydropyridin-3-yl)methanol (*ent*-20q)



$[\alpha]_D^{25}$ = + 42.3 (*c* 0.1, CH_2Cl_2). HPLC analysis: 18:82er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 88/12), flow rate (0.5 mL/min), t_R (major) = 13.397 min, t_R (minor) = 15.273 min].

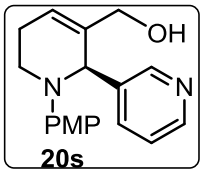
(*S*)-(1-(4-methoxyphenyl)-2-(pyridin-2-yl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20r)



20r

Dark red viscous liquid, (56 mg, 63% yield),^{1}H NMR ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33–2.37 (bs, 2H), 3.19–3.25 (m, 1H), 3.34-3.40 (m, 1H), 3.74 (s, 3H), 4.08 (m, 2H), 5.27 (s, 1H), 5.99 (t, J = 3.9 Hz, 1H), 6.76-6.80 (m, 2H), 6.82-6.83 (m, 2H), 7.16–7.19 (m, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 8.50 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.81, 43.93, 55.49, 63.71, 65.88, 114.48 (2C), 117.45 (2C), 120.86, 122.50, 124.11, 124.93, 136.86, 137.42, 148.07, 159.26, 161.77; IR (KBr)/cm^{-1} 3294, 3055, 2924, 2839, 1466, 1242, 1034; HRMS (ESI): Calcd for $C_{18}H_{20}N_2O_2$ (MH^+) 297.1603; Found:297.1608. $[\alpha]_D^{25}$ = – 111.5 (*c* 0.8, CH_2Cl_2). HPLC analysis: 91:9 er [Daicel Chiralpak-IB, *n*-hexane/2-propanol = 85/15), flow rate (0.5 mL/min), t_R (minor) = 22.747 min, t_R (major) = 28.847 min].

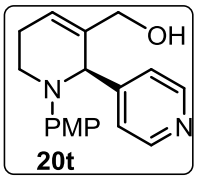
(*R*)-(1-(4-methoxyphenyl)-2-(pyridin-3-yl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20s)



20s

Red viscous liquid, (64 mg, 72% yield), ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.27–2.32 (m, 1H), 2.40–2.50 (m, 1H), 3.09–3.17 (m, 2H), 3.73 (s, 3H), 3.87 (d, J = 13.0 Hz, 1H), 3.99 (d, J = 12.9 Hz, 1H), 5.12 (s, 1H), 6.13 (s, 1H), 6.75 (d, J = 9.0 Hz, 2H), 6.84 (d, J = 9.1 Hz, 2H), 7.13–7.15 (m, 1H), 7.42–7.44 (m, 1H), 8.32 (s, 1H), 8.41 (m,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.70, 42.52, 55.37, 60.18, 64.41, 141.18 (2C), 121.29 (2C), 123.07, 124.44, 135.00, 136.63, 136.92, 143.86, 148.23, 149.69, 154.24; IR (KBr)/cm^{-1} 3410, 2924, 2862, 1651, 1582, 1512, 1242, 1034; HRMS (ESI): Calcd for $C_{18}H_{20}N_2O_2$ (MH^+) 297.1603; Found:297.1605. $[\alpha]_D^{25}$ = – 103 (*c* 0.4, CH_2Cl_2). HPLC analysis: 81:19 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 80/20), flow rate (1.0 mL/min), t_R (minor) = 19.082 min, t_R (major) = 22.508 min].

(*R*)-(1-(4-methoxyphenyl)-2-(pyridin-4-yl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20t)

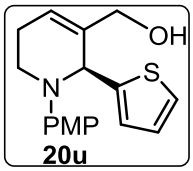


20t

Yellow viscous liquid, (67 mg, 76% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26–2.31 (m, 1H), 2.39–2.47 (m, 1H), 3.08–3.22 (m, 2H), 3.73 (s, 3H), 3.87 (d, J = 12.7 Hz, 1H), 3.98 (d, J = 12.8 Hz, 1H), 5.08 (s, 1H), 6.12 (t, J = 3.2 Hz, 1H), 6.74 (d, J = 9.1 Hz, 2H), 6.83 (d, J = 9.1 Hz, 2H), 7.05 (d, J = 6.0 Hz, 2H), 8.41 (d, J = 5.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.60, 42.79, 55.38, 61.26, 64.38, 114.17 (2C), 115.35, 118.22, 120.82 (2C), 123.89, 124.57, 136.73, 143.87, 148.52, 149.08, 154.08; IR

(KBr)/cm^{-1} 3711, 3040, 2916, 2847, 1512, 1458, 1260, 1188; HRMS (ESI): Calcd for $C_{18}H_{20}N_2O_2$ (MH^+) 297.1603; Found:297.1611. $[\alpha]_D^{25}$ = –105.9 (*c* 0.7, CH_2Cl_2). HPLC analysis: 96:4 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 80/20), flow rate (1.0 mL/min), t_R (minor) = 20.044 min, t_R (major) = 24.477 min].

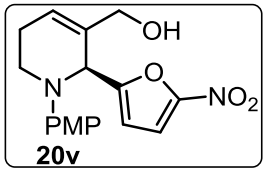
(*S*)-(1-(4-methoxyphenyl)-2-(thiophen-2-yl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20u)



20u

Reddish viscous oil,(48 mg, 53% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.24–2.29 (m, 1H), 2.43–2.52 (m, 1H), 3.21–3.24 (m, 2H), 3.75 (s, 3H), 4.02–4.09 (m, 2H), 5.41 (s, 1H), 6.03–6.05 (m, 1H), 6.66–6.68 (m, 1H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.83–6.84 (m, 1H), 6.87 (d, *J* = 9.2 Hz, 2H), 7.12–7.13 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.98, 41.06, 55.41, 57.89, 64.97, 114.13 (2C), 120.69 (2C), 123.85, 124.81, 126.12, 126.64, 138.29, 141.57, 144.02, 153.97; IR (KBr)/cm^{-1} 3493, 2924, 2854, 1651, 1512, 1242, 1034; HRMS (ESI): Calcd for $C_{17}H_{19}NO_2S$ (MH^+) 302.1214; Found: 302.1219. $[\alpha]_D^{25}$ = –123 (*c* 0.2, CH_2Cl_2). HPLC analysis: 86:14 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 90/10), flow rate (0.5 mL/min), t_R (minor) = 30.484 min, t_R (major) = 36.166 min].

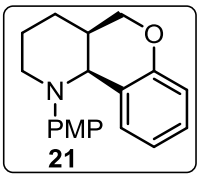
(*S*)-(1-(4-methoxyphenyl)-2-(5-nitrofuran-2-yl)-1,2,5,6-tetrahydropyridin-3-yl)methanol (20v)



20v

Dark red viscous liquid, (62 mg, 63% yield),^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28–2.35 (m, 2H), 3.22–3.25 (m, 2H), 3.64 (s, 2H), 3.77 (s, 3H), 4.11 (s, 1H), 5.86 (bs, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 6.98 (m, 2H), 7.27–7.30 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.03, 41.22, 55.48, 57.96, 65.05, 114.22 (2C), 120.89 (2C), 123.91, 124.84, 126.16, 126.63, 138.40, 141.83, 144.13, 154.04; IR (KBr)/cm^{-1} 3420, 2924, 2848, 1512, 1458, 1404, 1250, 1188; HRMS (ESI): Calcd for $C_{17}H_{18}N_2O_5$ (MH^+) 331.1294; Found: 331.1298. $[\alpha]_D^{25}$ = –146 (*c* 0.4, CH_2Cl_2). HPLC analysis: 86:14 er [Daicel Chiralpak-IA, *n*-hexane/2-propanol = 85/15), flow rate (0.5 mL/min), t_R (minor) = 25.996 min, t_R (major) = 30.493 min].

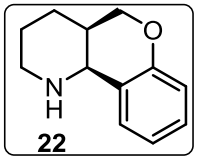
Synthesis of (4a*R*,10b*S*)-1-(4-methoxyphenyl)-1,3,4,4a,5,10b-hexahydro-2*H*-chromeno[4,3-*b*]pyridine (21)



21

To a stirred solution of compound **20j** (160 mg, 0.43 mmol) in dry EtOH (4 mL) was added 10% Pd/C (10 wt %) and purged with H_2 and stirred under H_2 at room temperature for 4 hrs. Reaction mixture was filtered through celite and washed with ethanol. Solvent was evaporated under vacuo and crude material was used for further oxidation without purification at this stage. This crude material was taken in DMF (3.0 mL) and added $Pd(OAc)_2$(18 mg, 20 mol%) and KO^{t}Bu (94 mg, 0.42 mmol) and PPh_3 (44 mg,0.4 equivalents) and degassed the reaction mixture with nitrogen for 20 minutes. This reaction mixture was heated at 110 ^oC for 4 hrs and monitored by TLC. The reaction was quenched with saturated $NaHCO_3$ solution (5.0 mL) and extracted with EtOAc (2 × 8 mL). The combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated under reduced pressure to give crude mass which was purified by silica gel column chromatography by using hexane:EtOAc, gave **21** (62 mg, 61%yield) as colorless viscous liquid.^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47–1.59 (m, 1H), 1.84–1.87 (m, 2H), 2.03–2.07 (m, 1H), 2.77 (m, 1H), 3.29–3.40 (m, 3H), 3.66 (s, 3H), 4.31 (d, J = 3.9 Hz, 1H), 6.63 (d, J = 9.1 Hz, 2H), 6.94–7.00 (m, 3H), 7.08 (m, 1H), 7.13–7.16 (m, 1H), 7.52–7.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.85, 27.62, 47.45, 55.15, 58.37, 61.89, 64.56, 113.65 (2C), 125.39 (2C), 127.11, 127.80, 128.61 (2C), 129.95 (2C), 133.70 (2C); IR (KBr)/cm^{-1} 2932, 1597, 1298, 1180, 1034; HRMS (ESI): Calcd for $C_{19}H_{21}NO_2$ (MH^+) 296.1650; Found: 296.1655. $[\alpha]_D^{25}$= –31.7 (*c* 0.4, CH_2Cl_2).

Synthesis of (4a*R*,10b*S*)-1,3,4,4a,5,10b-hexahydro-2*H*-chromeno[4,3-*b*]pyridine (22)

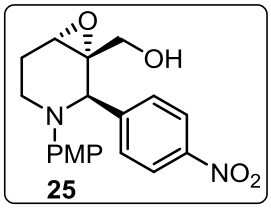


22

To a stirred solution of ceric ammonium nitrate (CAN) (441 mg, 0.8 mmol) in distilled H_2O (2.0 mL) at 0 °C was added compound **21** (95 mg, 0.32 mmol) in CH_3CN (3.0 mL) drop wise for 10 minutes. This reaction mixture was further stirred at rt for 1 hr and monitored by TLC. Once, compound **21** was consumed completely, reaction was quenched with saturated $NaHCO_3$ (5.0 mL) and extracted with EtOAc (3× 5 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure after filtration. The crude mas was purified through a small pad of silica gel column using hexane:acetone as eluting solvent, afforded **22** (46 mg, 75% yield) as colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41–1.52 (m, 2H), 2.02–2.07 (m, 2H), 2.62 (s, 1H), 2.76–2.83 (m,

1H), 3.16–3.20 (m, 1H), 3.27–3.38 (m, 2H), 3.58–3.65 (m, 1H), 4.07 (d, *J* = 3.8 Hz, 1H), 7.18–7.22 (m, 1H), 7.28–7.30 (m, 1H), 7.35 (dd, *J* = 7.9 Hz, *J* = 1.3 Hz, 1H), 7.61 (dd, *J* = 7.7 Hz, *J* = 1.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.31, 28.04, 48.15, 58.59, 64.95, 70.16, 125.23, 128.05, 128.56, 130.85, 132.36, 156.15; IR (KBr)/cm^{-1} 3433, 2932, 1597, 1350, 1103; HRMS (ESI): Calcd for $C_{12}H_{15}NO$ (MH^+) 190.1232; Found: 190.1235. $[\alpha]_D^{25}$ = –29.2 (*c* 0.1, CH_2Cl_2).

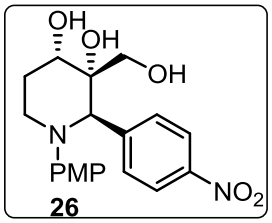
Synthesis of ((1*S*,2*R*,6*S*)-3-(4-methoxyphenyl)-2-(4-nitrophenyl)-7-oxa-3-azabicyclo[4.1.0] heptan-1-yl)methanol (25)



25

To a stirred solution of compound **20c** (64 mg, 0.19 mmol) in CH_2Cl_2 (2.0 mL) at 0 °C was added *m*-CPBA (56 mg, 0.38 mmol) predissolved in CH_2Cl_2(1.0 mL) through syringe. This reaction mixture was further stirred for 3 hr at the same temperature and monitored by TLC. Once, compound **20c** was consumed, reaction was stirred with $NaHCO_3$ solution (3.0 mL, 10 mol % sol.)for 10 minutes. This reaction mixture was extracted with CH_2Cl_2 (5.0 mL) and combined organic layer was washed with brine solution and dried over Na_2SO_4. The crude mass after concentrated under vacuo was purified through column chromatographyby unsing hexane/EtOAc as eluting solvents, which afford compound **25** (50 mg, 75% yield) as a colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (d, *J* = 4.2 Hz, 1H), 3.23 (d, *J* = 11.6 Hz, 1H), 3.44 (d, *J* = 11.7 Hz, 1H),3.69–3.78 (m, 6H), 4.63–4.70 (m, 1H), 5.02 (s, 1H), 5.40 (s, 1H), 6.68 (d, *J* = 9.4 Hz, 2H), 7.03 (d, *J* = 8.9 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.84–7.95 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.17, 32.70, 43.34, 55.70, 58.15, 69.66, 72.58, 114.92 (2C), 121.97 (2C), 123.75 (2C), 130.25 (2C), 137.58, 144.45, 147.76, 155.05; IR (KBr)/cm^{-1} 3433, 2916, 2854, 1713, 1574, 1381, 1257, 1080, 756; HRMS (ESI): Calcd for $C_{19}H_{20}N_2O_5$ (MH^+) 357.1450; Found: 357.1455. $[\alpha]_D^{25}$ = + 43.8 (*c* 0.2, CH_2Cl_2).

Synthesis of (2*R*,3*S*,4*S*)-3-(hydroxymethyl)-1-(4-methoxyphenyl)-2-(4-nitrophenyl) piperidine-3,4-diol (26)

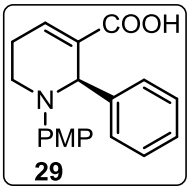


26

To a stirred solution of compound **20c** (60 mg, 0.18 mmol) in acetone (2.5 mL) and H_2O (0.5 mL) was added 4-Methylmorpholine *N*-oxide (NMO) (32 mg, 0.27 mmol) and OsO_4 (20 mol %, 1.76 mL, 0.02 M solution in *tert*-BuOH). This reaction mixture was stirred at room temperature for 12

hrs and monitored by TLC. The reaction mixture was evaporated under reduced pressure, once **20c** was completely consumed. The resulting mass was stirred with EtOAc (10 ml) and saturated $NaHCO_3$ (8.0 mL) for 10 minutes. Organic layer was separated and the aqueous layer was again extracted with EtOAc (2 × 10 mL). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure after filtration. The resulting mass was purified through column chromatography using hexane/EtOAc as eluting solvents, which afforded **26** (42 mg, 65 % yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94–1.98 (m, 1H), 2.27–2.35 (m, 1H),3.11–3.21 (m, 2H), 3.56 (d, J = 11.6 Hz, 1H), 3.67 (s, 3H), 3.73 (bs, 1H), 3.75–3.79 (m, 1H), 4.19 (t, J = 3.7 Hz, 1H), 4.65 (s, 1H), 6.65 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 7.41 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 29.44, 51.47, 55.22, 63.94, 67.55, 69.20, 73.56, 114.14 (2C), 122.67 (2C), 125.11 (2C), 130.69 (2C), 144.11, 145.21, 146.74, 156.02; IR (KBr)/cm^{-1} 3441, 2939, 1597, 1520, 1350, 1250, 1103; HRMS (ESI): Calcd for $C_{18}H_{22}N_2O_6$ (MH^+) 375.1556; Found: 375.1560. $[\alpha]_D^{25}$ = – 61.5 (*c* 0.15, CH_2Cl_2).

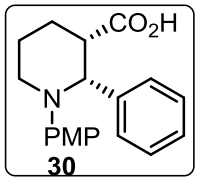
Synthesis of (*R*)-1-(4-methoxyphenyl)-2-phenyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid (29)



29

To a stirred solution of compound **20q** (81 mg, 0.2 mmol) in acetonitrile (1.5 mL) and H_2O (0.5 mL) at 0 °C, was added slowly a freshly prepared solution (1.5 mL) of oxidizing agents [*prepared through reported procedure,*[97] *(2.3 mg of $CrO_3$and 1.14 grams of H_5IO_6), in H_2O (12.0 mL*)] over a period of 30 minutes. The combined mixture was further stirred for additional 1 hrat rt and monitored by the TLC. The reaction was extracted with CH_2Cl_2 (2 × 10 mL), once **20q** was over. The combined organic fractions are passed through a small pad of Na_2SO_4 and concentrated under reduced pressure. The crude mass was purified through preparative TLC technique by eluting with CH_2Cl_2, to afford **29** (57 mg, 68%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.38 (m, 1H), 2.60–2.73 (m, 1H), 3.20–3.28 (m, 1H), 3.30–3.35 (m, 1H), 3.76 (s, 3H), 5.23 (s, 1H), 6.12 (s, 1H), 6.76 (d, J = 9.1 Hz, 2H), 6.89 (d, J = 9.1 Hz, 2H), 7.01 (dd, J = 8.0, 1.4 Hz, 2H), 7.18–7.26 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ29.65, 44.12, 55.54, 63.54, 114.61 (2C), 123.49 (2C), 127.98, 128.67, 129.16, 130.46, 131.40, 131.74, 133.31, 134.18, 141.74, 160.01, 171.00; IR (KBr)/cm^{-1} 3441-3061 (br), 2939, 1690, 1582, 1512, 1126;HRMS (ESI): Calcd for $C_{19}H_{19}NO_3$ (MH^+) 310.1443; Found: 310.1439.$[\alpha]_D^{25}$ = – 127.4 (*c* 0.25, CH_2Cl_2).

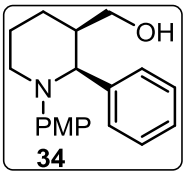
Synthesis of (2*R*,3*S*)-1-(4-methoxyphenyl)-2-phenylpiperidine-3-carboxylic acid (30)



30

To a stirred solution of compound *ent*-**20q** (96 mg, 0.32 mmol) in dry EtOH (4 mL) was added 10% Pd/C (10 wt %) and purged with H_2 and stirred under H_2 at room temperature for 4 hrs. Reaction mixture was filtered through celite and washed with ethanol. Solvent was evaporated under vacuo and crude material was used for further oxidation without purification at this stage. The oxidation of crude saturated *syn*-alcohol to corresponding acid was carried out by following the previous procedure, similar to compound **29**, to afford **30** (66 mg, 66% yield) after two steps. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86–1.94 (m, 1H), 2.01–2.08 (m, 2H), 3.25–3.30 (m, 2H), 3.43–3.46 (m, 2H), 3.66 (s, 3H), 3.92 (d, J = 3.9 Hz, 1H), 6.63 (d, J = 9.1 Hz, 2H), 7.04 (d, J = 8.5 Hz, 2H), 7.15 (m, 3H), 7.38–7.42 (m, 2H);^{13}C NMR (75 MHz, $CDCl_3$) δ 22.68, 27.19, 29.68, 42.65, 55.24, 64.90, 113.85 (2C), 124.83, 127.32, 127.90 (2C), 128.28, 128.73, 131.23, 132.44, 135.92, 141.29, 170.16; IR (KBr)/cm^{-1} 3433–3063 (br), 2939, 1690, 1589, 1173, 1034; HRMS (ESI): Calcd for $C_{19}H_{21}NO_3$ (MH^+) 312.1599; Found: 312.1592. $[\alpha]_D^{25}$ = + 49.4 (*c* 0.1, CH_2Cl_2).

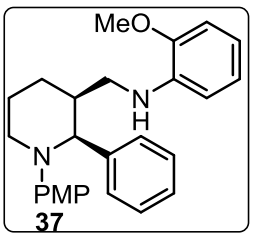
Synthesis of ((2*S*,3*R*)-1-(4-methoxyphenyl)-2-phenylpiperidin-3-yl)methanol (34)



34

Compound **20q** (140 mg, 0.32 mmol), was reduced by following previous procedure and purified through column chromatography to afford **34** as colorless viscous liquid with 90% yield (126 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.62–1.69 (m, 2H), 1.83 (d, J = 6.4 Hz, 2H), 2.61–2.70 (m, 2H), 3.00–3.09 (m, 2H), 3.50–3.55 (m, 2H), 3.75 (s, 3H), 3.76–3.83 (m, 1H), 6.56 (d, J = 9.0 Hz, 2H), 6.78 (d, J = 8.9 Hz, 2H), 7.16–7.22 (m, 3H), 7.29 (t, J = 6.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.51, 27.42,45.96, 55.18, 56.60, 65.27, 67.46, 113.66 (2C), 125.11, 126.72 ,128.02 (2C) ,128.47 (2C), 139.24 , 142.13, 146.05, 155.21; HRMS (ESI): Calcd for $C_{19}H_{23}NO_2$ (MH^+) 298.1808, Found: 298.1813. $[\alpha]_D^{25}$= – 56.3 (*c* 0.1, CH_2Cl_2).

Synthesis of 2-methoxy-*N*-(((2*S*,3*S*)-1-(4-methoxyphenyl)-2-phenylpiperidin-3-yl)methyl) aniline (37)



37

To a stirred solution of **34** (90 mg, 0.3 mmol) in dry CH_2Cl_2 (2.0 mL) at rt was added Et_3N (168 µL, 1.2 mmol) and TsCl (69 mg, 0.36 mmol) in dry CH_2Cl_2 (1.5 mL) by syringe. The resulting mixture was further stirred for 6 hrs at the same temperature and monitored by TLC. The reaction was quenched with saturated $NaHCO_3$ (3.0 mL) and extracted with CH_2Cl_2 (2 ×

5 mL). The combined organic layer was dried over $Na_2SO_4$and concentrated in reduced pressure to give crude product, which was used further without isolation. The crude mass was taken in dry EtOH (3 mL) and added *o*-anisidine **36** (74 mg, 0.6 mmol) and further refluxed for additional 4 hrs. Once the reaction is over by TLC, EtOH was evaporated under reduced pressure and resulting residue was purified by column chromatography to afforded **37** (83 mg, 68% yield) as colorless viscous liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58–1.75 (m, 4H), 2.10–2.13 (m, 1H), 2.93–3.00 (m, 1H), 3.12–3.16 (m, 1H), 3.49–3.57 (m, 2H), 3.78 (s, 3H), 3.86 (s, 3H), 5.04 (d, *J* = 3.6, 1H), 6.47–6.49 (m, 1H), 6.56–6.60 (m, 1H), 6.72–6.76 (m, 2H), 6.78–6.81 (m, 2H), 6.84 (d, *J* = 9.2, 2H), 6.91(d, *J* = 9.2 Hz, 2H), 6.99–7.03 (m, 1H), 7.14 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.28, 24.51, 31.47, 42.12, 46.55, 55.39, 55.75, 56.69, 110.37, 113.62, 114.80 (2C), 115.00, 115.94, 117.00, 118.46, 120.11, 121.03, 127.61 (2C), 128.07, 136.08, 144.81, 145.62, 147.28, 151.61; IR (KBr)/cm^{-1} 3393, 2932, 2831, 1598, 1512, 1366, 1180, 1034; Calcd for $C_{26}H_{30}N_2O_2$ (MH^+) 403.2385; Found: 403.2389. $[\alpha]_D^{25}$ = – 54.6.0 (*c* 0.15, CH_2Cl_2).

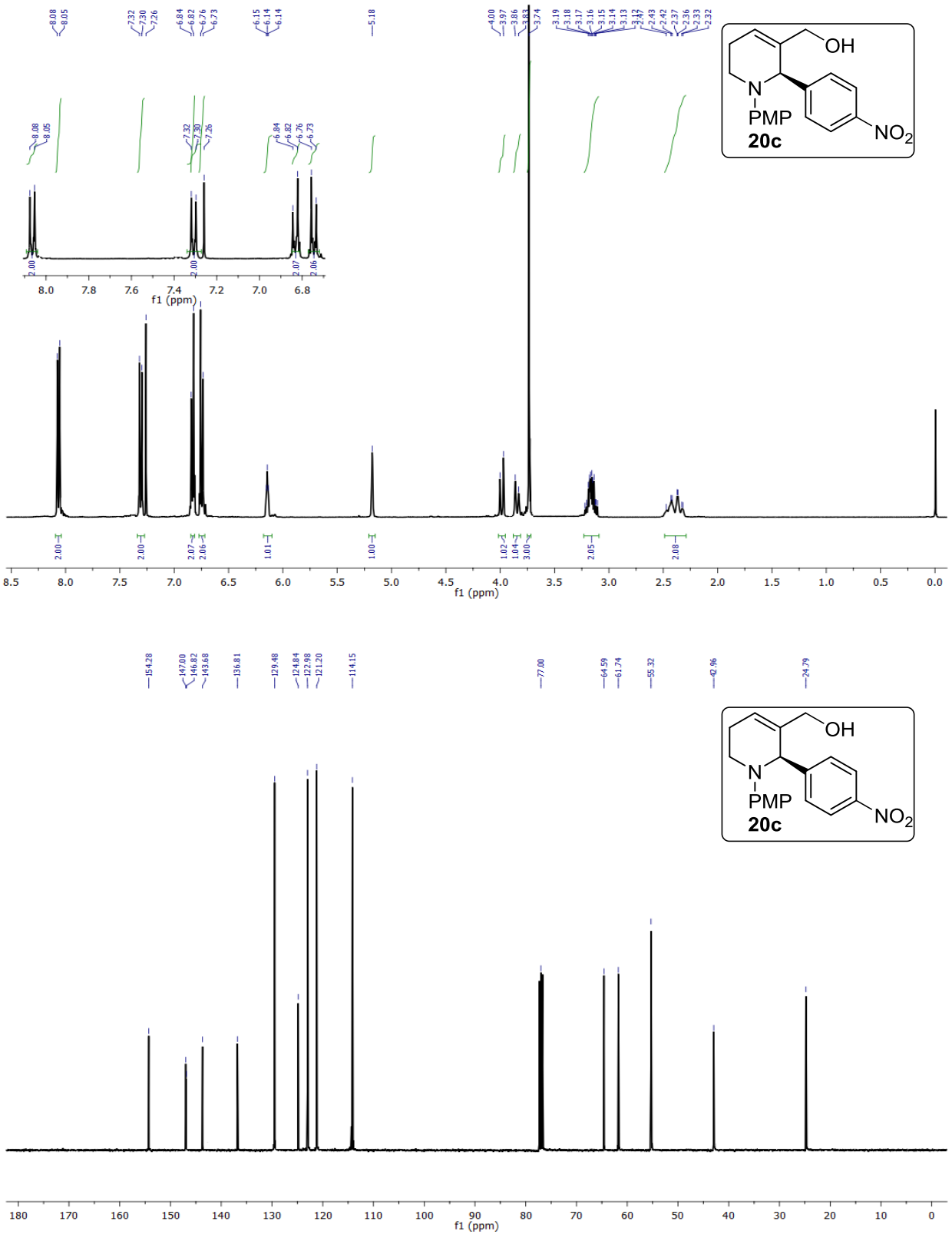
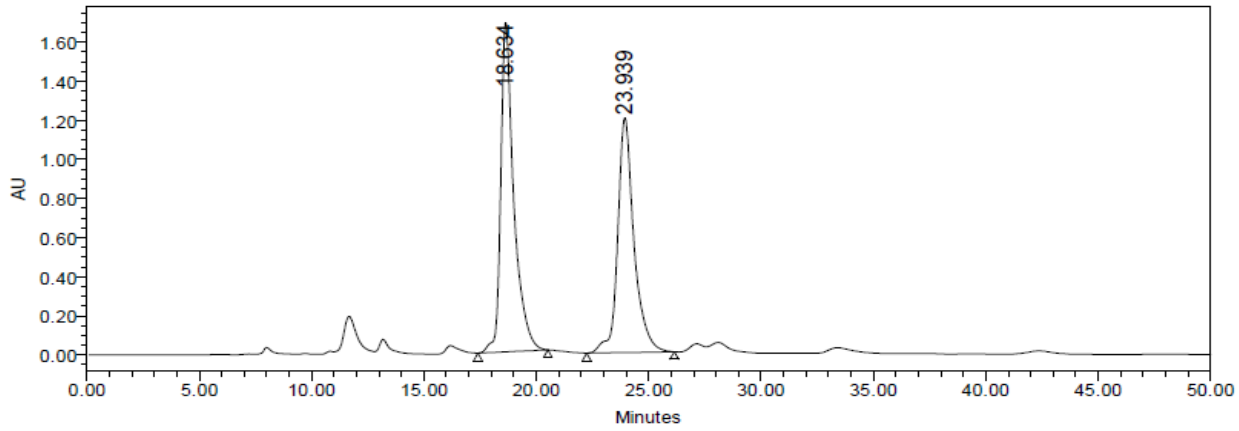


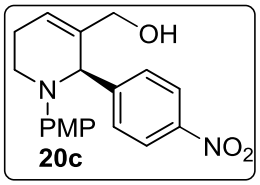
Figure 4.2 ^{1}H and ^{13}C NMR spectra of **20c**

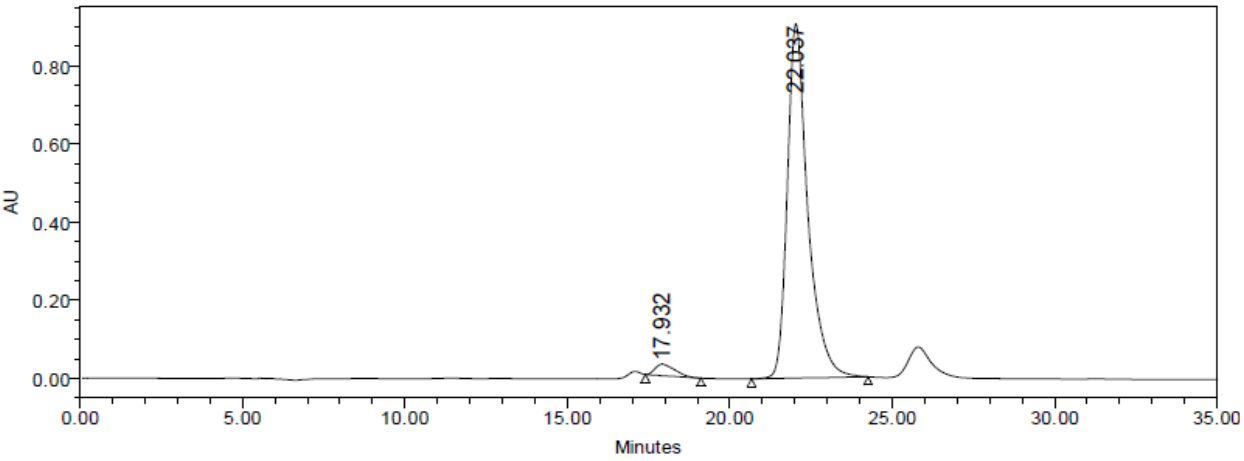


Channel: 2998; Processed Channel: PDA 250.0 nm; Result Id: 7863; Processing Method: 4 NITRO RACEMIC THP

Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	18.634	67961973	52.87	1684220
2	PDA 250.0 nm	23.939	60575125	47.13	1200481





Channel: 2998; Processed Channel: PDA 250.0 nm; Result Id: 7865; Processing Method: 4 NITRO CHIRAL THP

Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	17.932	1239998	3.01	29304
2	PDA 250.0 nm	22.037	39964344	96.99	907207

Figure 4.3 HPLC chromatogram of **20c**

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Chapter - 5

Proline Catalyzed Enantio- and Diastereoselective Synthesis of Isoquinuclidines

5.1 Introduction:

The functionalized isoquinuclidines have broad anti-malarial activities.[1] The isoquinuclidine based dioscorine is a toxic central nervous system depressant and a modulator of the nicotinic acetylcholine receptor. Isoquinuclidines are considered as important scaffolds found in several natural products and drug molecules.[2-10] Because of the unique structural complexity and biological activities, the synthesis of these molecules is attaining more interest by the synthetic chemists. Since these molecules have broad scope of activities, Several methods are available in the literature to synthesize such kinds of molecules. A complex biosynthetic approach revealed, [11] how difficult it is to access the isoquinuclidines in enantiomerically pure form. Therefore, the asymmetric routes are most attractive and highly desirable for the researchers because of the unique stereochemical outcome of the isoquinuclidines, and these chiral isoquinuclidines may possess interesting biological activities as well as find application for the synthesis of complex alkaloids and drug molecules.

Isoquinuclidine derivatives are valuable intermediates in alkaloid synthesis, especially *Iboga*-type indole alkaloids of which (+)-catharanthine[26] is of special interest because of its role as biogenetic and synthetic precursors of vinblastine[38] and related antitumoral bisindole alkaloids. Despite the progress in the synthesis of isoquinuclidines, only few methods for the asymmetric synthesis of functionalized isoquinuclidines have been reported.

It is very worthwhile to explore a new method for the synthesis of optically active isoquinuclidines. These azabicyclic compounds are key synthetic intermediates of *iboga*-alkaloides. The Diels–Alder reaction between chiral 1,2-dihydropyridines and olefins may be the most capable method for this purpose. However, there have been few Diels-Alder reactions between chiral 1,2-dihydropyridines and olefins explored so far. This is due to the limited availability of chiral 1,2-dihydropyridines and dienophiles. This background encouraged us to develop a method where the chiral 1,2-dihydropyridines usable as suitable dienes for the Diels-Alder reaction with appropriate dienophiles. In our continuing study on the easy synthesis of chiral 1,2-DHPs, we thought to explore for the stereoselective [4+2] Diels-Alder reaction for the synthesis of isoquinuclidines. Few biologically important isoquinuclidines are shown in **figure 5.1.**

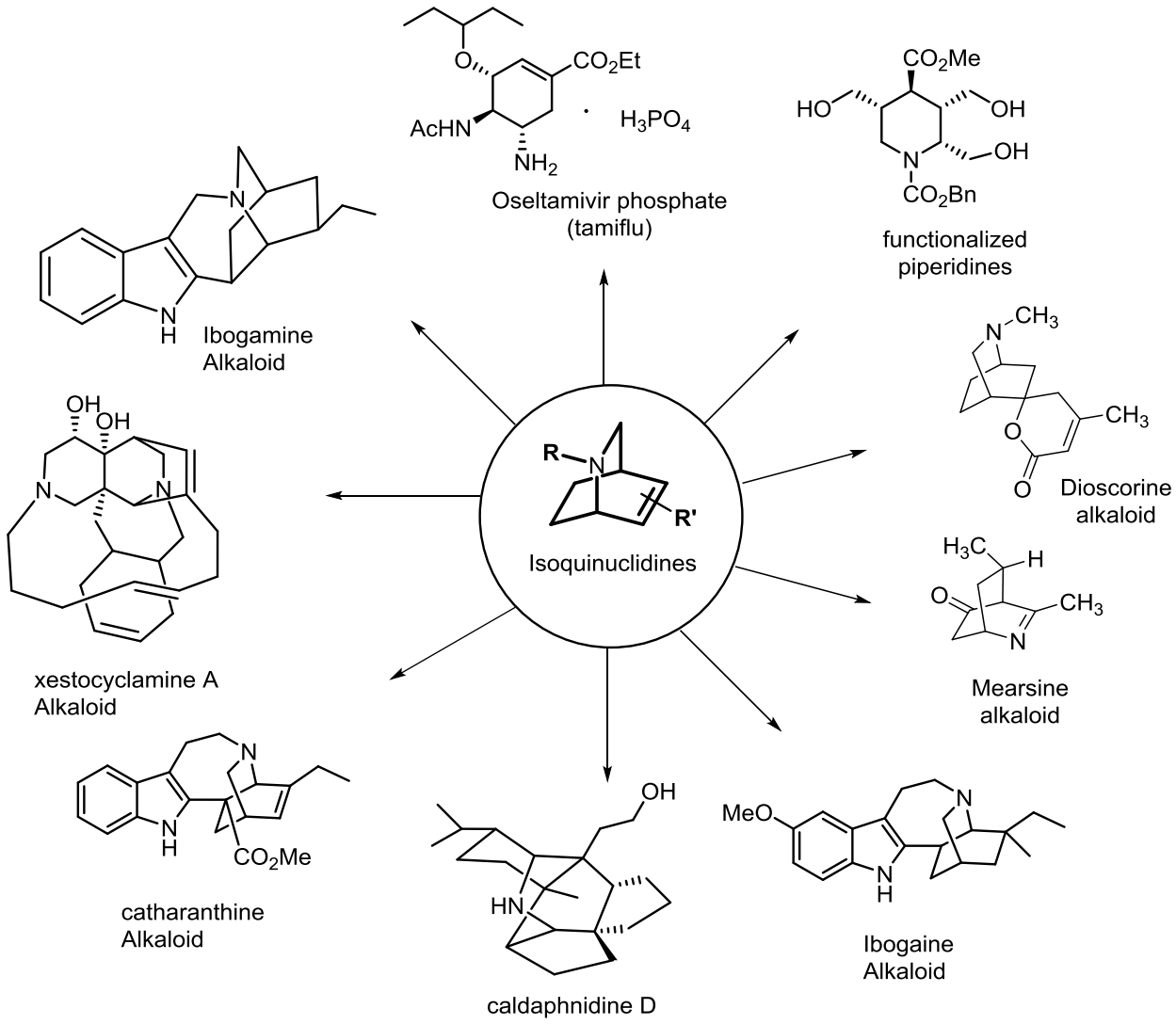
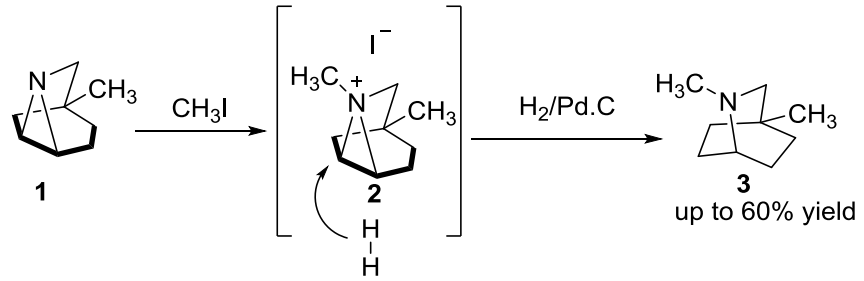


Figure 5.1 Synthetic utility of isoquinuclidines towards natural products and drugs

Few general approaches are reported for the synthesis of isoquinuclidines:

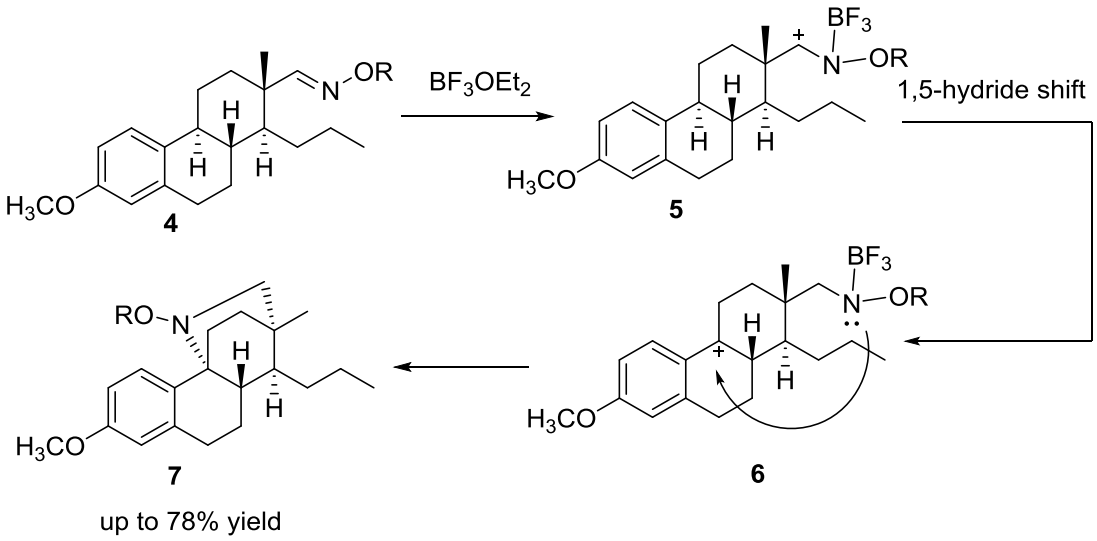
a) Stereochemical controlled reaction
b) Trifluoro boro etharate catalytic reaction
c) Tropinone desimmetrization reaction

(a) One of methods[12-15] involves this stereochemically controlled rearrangement approach for the synthesis of isoquinuclidines **3** is described in **scheme 5.1**. This approach involved as a regio-selective catalytic hydrogenation of the bicyclic ionic intermediate **2** resulted a stable bicyclic isoquinuclidine which was reported by T. Okumura.[14]



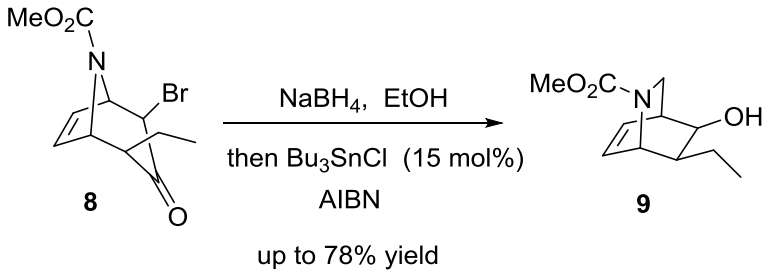
Scheme 5.1 Stereochemical controlled synthesis of isoquinuclidines

(b) Lewis acid (Trifluoroboroetharate) catalyzed intramolecular hydro-*n*-alkylation of oxime ethers **4**, for the synthesis of isoquinuclidines **7** *via* domino 1,5-hydride shift/cyclization was reported by E. Frank in good yields as shown in **Scheme 5.2**.[16]



Scheme 5.2 Lewis acid catalytic approach for the synthesis of isoqunuclidines

(c) Desymmetrization of tropenone **8** for the synthesis of isoquinuclidines **9** was reported by Hodgson group.[17] This strategy involved via an interesting homo allylic radical rearrangement of the *in situ* generated allylic radical followed by cyclization producing the isoquinuclidines **9**.



Scheme 5.3 Tropinone desymmetrization for the synthesis of isoquinuclidines

5.2 Diels-Alder Reactions:

In addition to the methods mentioned above, which require several synthetic steps, two general and quick approaches are also reported in literature. These methods for the synthesis of isoquinuclidines involves cycloaddition methods in particular, the Diels-Alder reactions are most important for the synthesis of isoquinuclidines because of atom economy. Depends on diene and dienophile, these [4+2] Diels-Alder reactions are further categorized into two types as shown in **figure 5.2.**

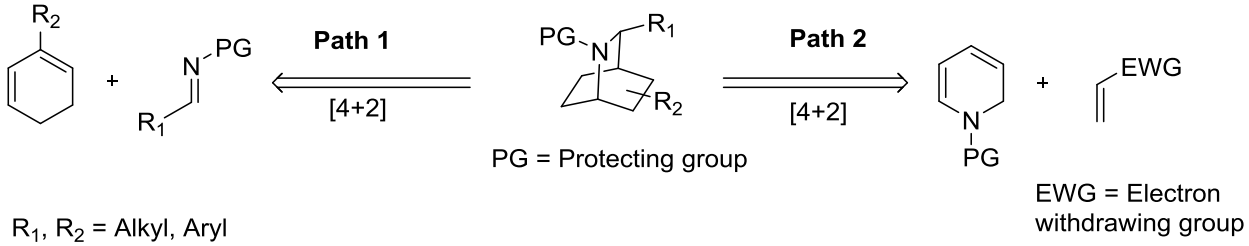


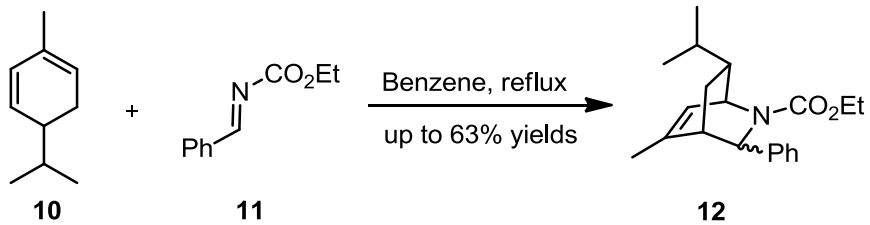
Figure 5.2 [4+2] Diels-Alder disconnection approaches

Path 1: [4+2] cycloaddition of cyclohexadienes and imines

Path 2: [4+2] cycloaddition of 1,2-dihydropyridines and alkenes

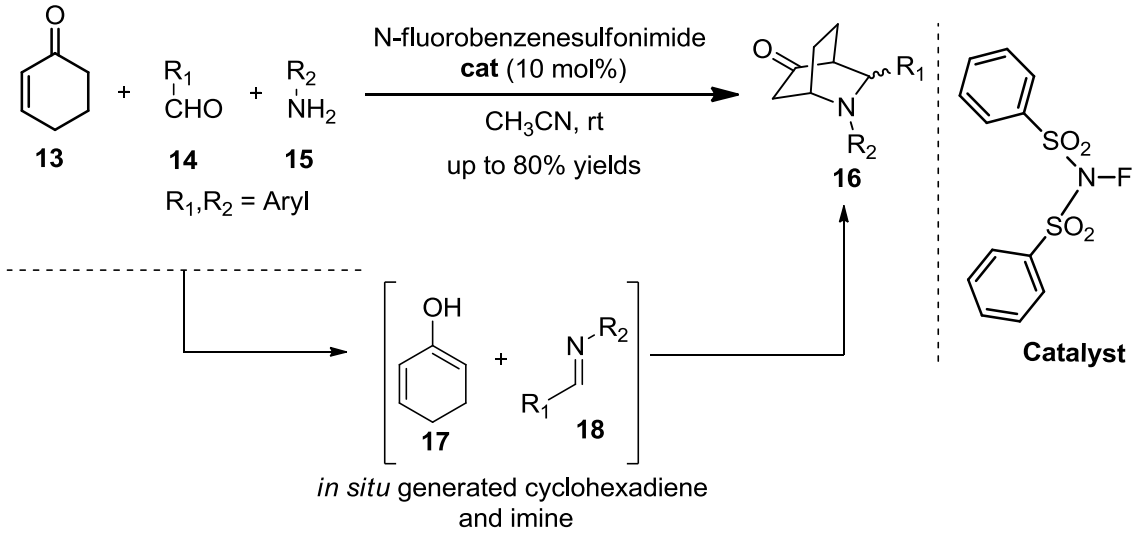
5.2.1 Path 1: [4+2] cycloaddition of cyclohexadienes and imines: [4+2] cycloaddition between cyclohexadienes and imines is a versatile method for the synthesis of isoquinuclidines. The following efforts have been described in this direction through staichiometric and catalytic versions. These methods reported for the synthesis of isoquinuclidines starting from cyclohexadienes and imines are explained here.

(i) The initial studies in this direction proceeded through stoichiometric [4+2] Diels–Alder reaction of preformed cyclohexadienes **10** and imines **11** under heating conditions which resulted the corresponding isoquinuclidines **12** in good yields which was reported by Krow group. **[18,19]**



Scheme 5.4 [4+2] cycloaddition of imines with cyclohexadienes**[18]**

(ii) When we talk about catalytic methods for isoquinuclidines, the N-fluorobenzenesulfonimide catalyzed multicomponent reaction involving *in situ* generated imines **18** and cyclohexadienes **17** for Aza [4+2] cycloaddition reaction for the synthesis of isoquinuclidines was recently developed by Z. Guan and cowerkers.[20] The resulting product **16** was obtained as a mixture of endo, exo isomers in good yields as shown in **Scheme 5.5**.



Scheme 5.5 Catalytic multicomponent approach of [4+2] Diels – Alder reaction of imines with cyclohexadienes [20]

(iii) Recently, asymmetric amine catalysis has been actively involved in [4+2] cycloaddition reaction between *in situ* generated cyclohexadiene and imine.[21,22] In this direction, different research groups have studied this reaction. However, the basic concept of this amine catalyzed [4+2] cycloaddition remains common as shown in **Figure 5.3.** Here, a chiral amine catalyst mediated cycloaddition of *in situ* generated cyclohexadienes (***TS-A***) with imines **18** proceed through enantioselective [4+2] Aza-Diels-Alder reaction to form optically pure isoquinuclidines **19**.[23-26] Recently, Yang group[23] reported the asymmetric synthesis of isoquinuclidines using a chiral amine **20** catalyzed [4+2] Diels-Alder reaction of *in situ* generated diene from cyclohexenone **12** with imines **18** in good yields and excellent enantioselectivities as shown in (equation 1**, Figure 5.3**). Another similar approach was reported by Còrdova group[25] using proline as a catalyst for asymmetric [4+2] Diels-Alder reaction of cyclohexadienes with *in situ* generated imines **18** for the synthesis of isoquinuclidines **23** (equation 2, **Figure 5.3**).

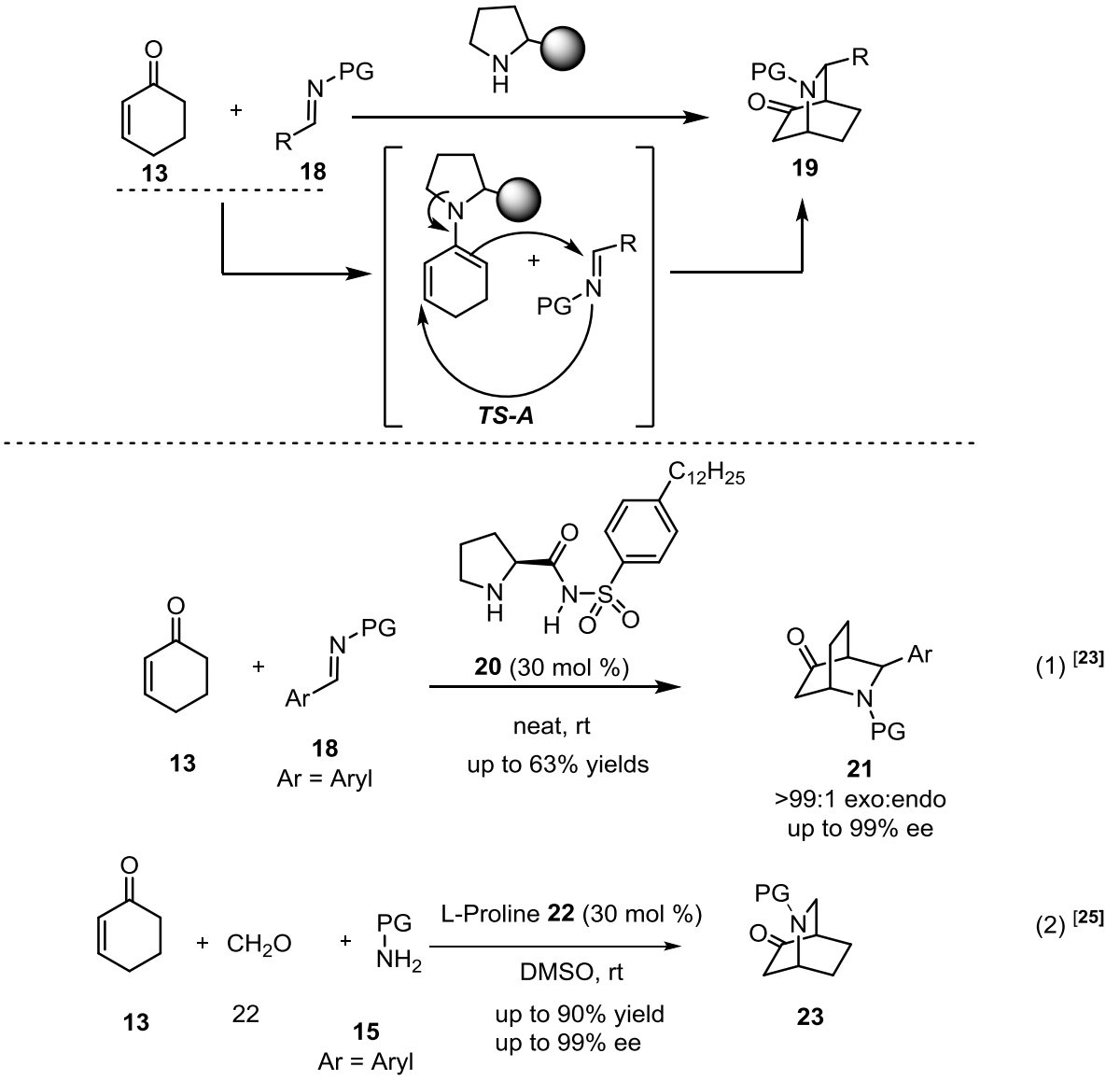


Figure 5.3 Catalytic asymmetric [4+2] cycloaddition of cyclohexadienes with imines

Path 1 (**Figure 5.2**) strategy appears to be a direct and simple method for the synthesis of isoquinuclidines. However, the main drawback of the above discussed [4+2] cycloaddition reactions of cyclohexadienes and imines was the generation of Baylis-Hillman side products and the appreciable yields are restricted to limited substrates.

5.2.2 Path 2: [4+2] cycloaddition of 1,2-dihydropyridines and activated alkenes:

The [4+2] cycloaddition involving 1,2-dihydropyridines as dienes, with activated alkenes as dienophiles is a resourceful route for the synthesis of isoquinuclidines.[27-30] Since we are

particularly interested in the asymmetric synthesis of isoquinuclidines, we focused particularly on the asymmetric methodologies for the synthesis of isoquinuclidines involving 1,2-dihydropyridines as dienes and activated alkenes as dienophiles. Depending on the chiral substrates used in a synthetic strategy for accessing isoquinuclidines, these methods are further subdivided into three types:

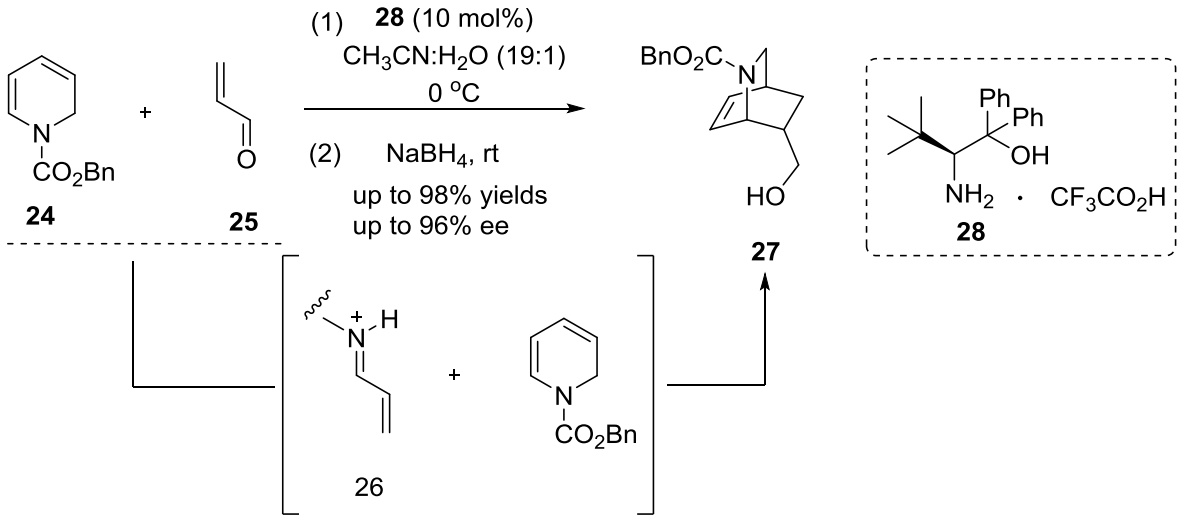
(i) Catalytic asymmetric [4+2] cycloadditions between 1,2-DHPs and alkenes

(ii) Asymmetric [4+2] cycloadditions involving chiral alkenes as dienophiles

(iii) Asymmetric [4+2] cycloadditions involving chiral 1,2-dihydropyridines as dienes

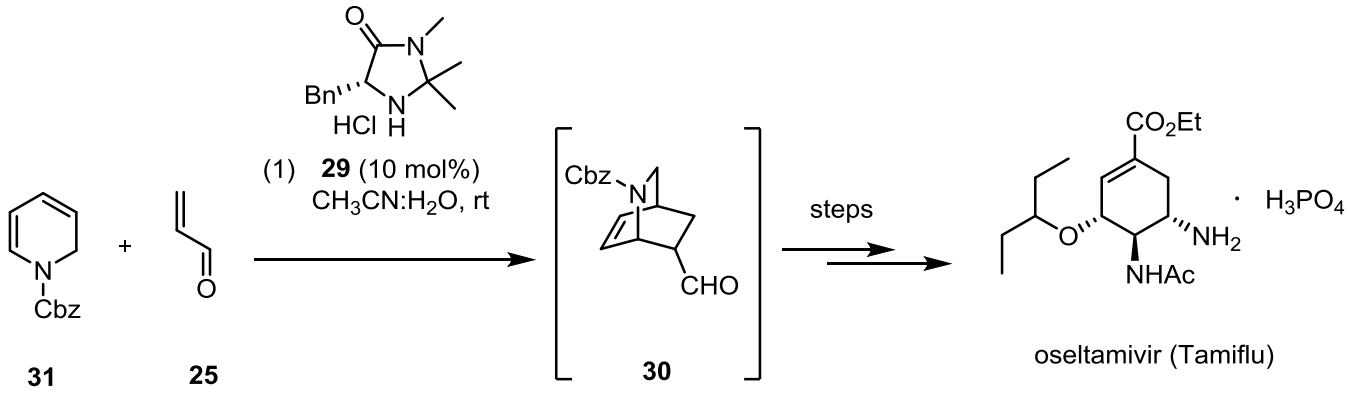
(i) Catalytic asymmetric [4+2] cycloadditions between 1,2-DHPs and alkenes:

The chiral catalyst plays major role in the [4+2] cycloaddition by imparting a chiral transition state in the reaction when associated with any of the diene or dienophile resulting the stereoselective outcome of the isoquinuclidines.[31-39] The most recent effort in this direction was done by E. Kwon *et al.,*[31] as well as a seminal report from H. Nakano group.[39] These strategies involved an organocatalytic enantioselective [4+2] cycloaddition of 1,2-DHPs **24** with the activated alkenes **25** followed by *in situ* reduction with the sodium borohydride in the same pot produced the functionalized isoquinuclidines **27** in excellent yields and selectivities. This kind organocatalytic asymmetric strategies for the synthesis of chiral isoquinuclidines are very important because of atom economical and environmental concerns.



Scheme 5.6 catalytic asymmetric [4+2] cycloaddition of 1,2-DHPs and dienophiles [31]

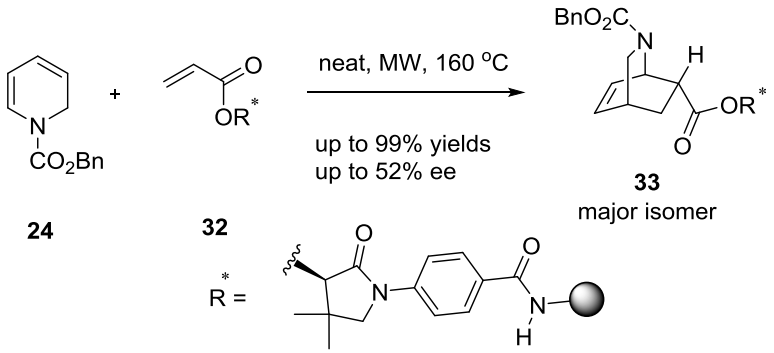
Fukuyama utilized this type of organocatalytic strategy for the synthesis of Oseltamivir drug.[37] The developed strategy involved an organocatalytic asymmetric [4+2] cycloaddition of 1,2-DHPs **31** with the activated alkenes **25** producing functionalized isoquinuclidines **30** followed by the construction of oseltamivir drug synthesis as shown in **Scheme 5.7.**



Scheme 5.7 Amine catalyzed asymmetric [4+2] cycloaddition of 1,2-DHPs and activated alkenes [37]

(ii) Asymmetric [4+2] cycloadditions involving chiral alkenes as dienophiles:

Choosing chiral dienophiles for [4+2] cycloaddition with 1,2-DHPs is an alternative strategy to the chiral catalyst for the synthesis of isoquinuclidines. Only few reports found in the literature for such kind of transformations involving chiral dienophiles.[40,41] A recent report from M. Calmes group revealed a resin supported chiral enone dienophile **32** was prepared by linking to a chiral cyclic amide moiety and performed the asymmetric Diels – Alder reaction with 1,2-DHPs **24**. Unfortunately they ended up with isoquinuclidines having moderate selectivity (only up to 52% ee).[40]

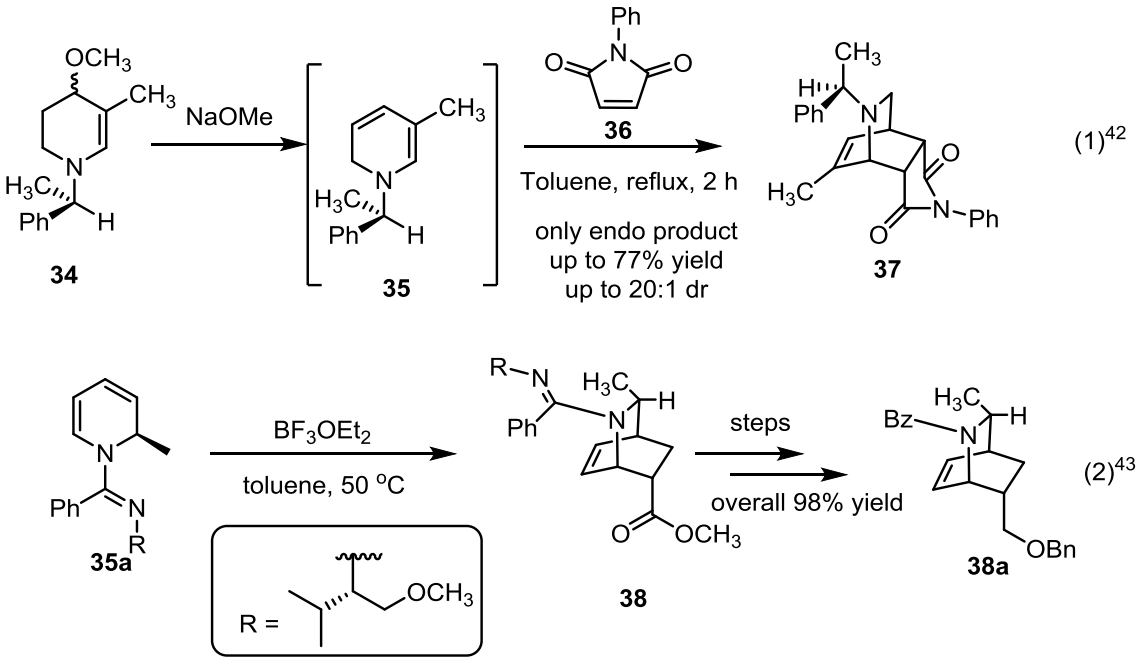


Scheme 5.8 [4+2] cycloaddition of chiral dienophiles with 1,2-DHPs[40]

This strategy involved a tedious procedure to resin functionalized chiral moiety incorporation to the dienophile and the protocol produced desired isoquinuclidines in moderate amount among the multiple regio isomers.

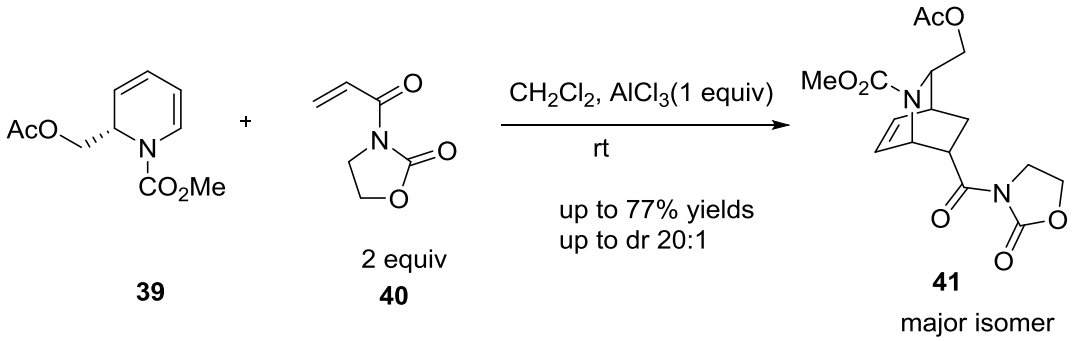
(iii) Asymmetric [4+2] cycloadditions involving chiral 1,2-dihydropyridines as dienes:

The Diastereoslective [4+2] cycloadditions involving chiral 1,2-DHPs as dienes is an interesting method to prepare isoquinuclidines.[42,43] Few methods utilized the 1,2-DHPs which are N-protected with chiral moiety is exemplified in **Scheme 5.9,** Eq.1.[42] This method involved as a diastereoselective [4+2] Diels-Alder reaction of chiral 1,2-DHPs **35** with the activated alkene **36** produced the chiral endo isoquinuclidines **37** in good yields and selectivities which was reported by Marazanoc group as shown in **Scheme 5.9**. A similar report was found by using DHPs with chiral protecting group in presence of lewis acid produced the isoquinuclidines **38** in good yields, Scheme 5.9, Eq.2[43]



Scheme 5.9 [4+2] cycloaddition involving 1,2-DHPs with chiral protecting group

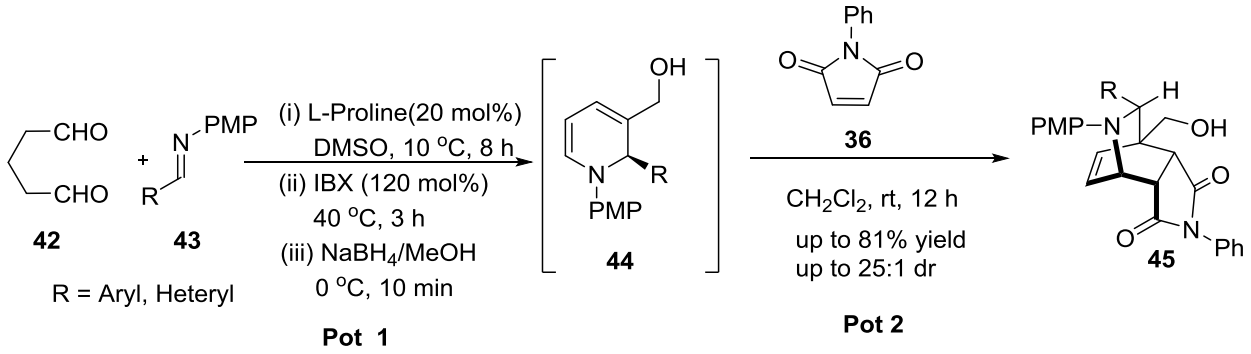
Despite the difficulty for the synthesis of chiral 1,2-DHPs, this moiety has been used as diene for diastereoselective [4+2] Diels-Alder reaction with dienophiles to prepare chiral isoquinuclidines.[44-46] Onomura group reported that, an enantiopure 1,2-DHPs **39** underwent the [4+2] Diels-Alder reaction with suitable dienophiles **40** which produced the corresponding chiral isoquinuclidines **41** in good yields and selectivities as shown in **Scheme 5.10**.



Scheme 5.10 [4+2] cycloaddition of enantiopure 1,2-DHPs with dienophiles[44]

5.3 Results and discussion:

It is clear from the literature analysis that, the synthesis of isoquinuclidines is gaining increasing attention due to its importantance in biologically active compounds. Therefore the development of new easy method for the asymmetric synthesis of isoquinuclidines from easily available materials is always welcome. In this direction, we have developed an organocatalytic enantio- and diastereo-selective synthesis of isoquinuclidines **45** from glutaraldehyde **42** and imine **43** through two pot tandem process without isolation at intermediate stage as shown in **scheme 5.11.**



Scheme 5.11 Enantio- and diastereoselective [4+2] cycloaddition for the synthesis of isoquinuclidines

Recently, we developed an easy and rapid access to chiral 1,2-DHPs **46** from easily available substrates such as glutaraldehyde and imine.[47] Further, we anticipated these chiral 1, 2-dihydro pyridines **46** could be used for diastereoselective [4+2] Diels-Alder reaction with highly reactive dienophile **36** which could ultimately lead to isoquinuclidines **47.** Having this idea in mind, diastereoselective [4+2] cycloaddition reaction between our previous isolated product 1,2-DHP **46** and activated alkene **36** was attempted under different conditions as shown in **Table 5.1.** The reaction failed to give expected product **47** in any conditions utilized at even high temperature

(entry 7, T**able 5.1**) or even under catalyst mediated Diels-Alder reaction in different solvent systems (entry 3,4,5, **Table 5.1**). Initially we thought that, presence of aldehyde group at C3 position of **46** may facilitate the reaction by pulling the ring electron density, and making the ring as 1, 4-carbon dipole at C3 and C6 positions of dihydropyridine **46**. But in practical, the idea did not work as shown in T**able 5.1**. In fact, the dihydropyridine **46** used to get decompose, when acetic acid (entry 3, **Table 5.1**) and silver triflate (entry 4, **Table 5.1**) were used as additives.

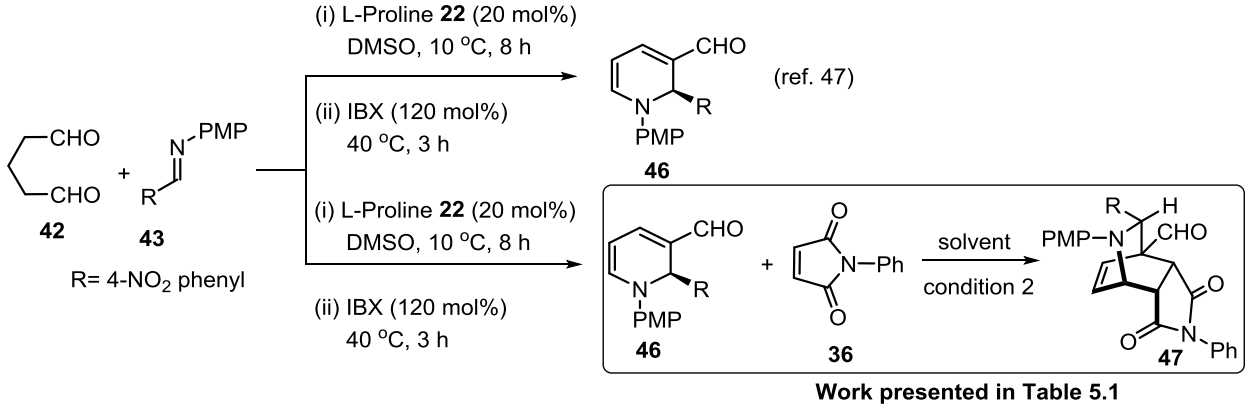
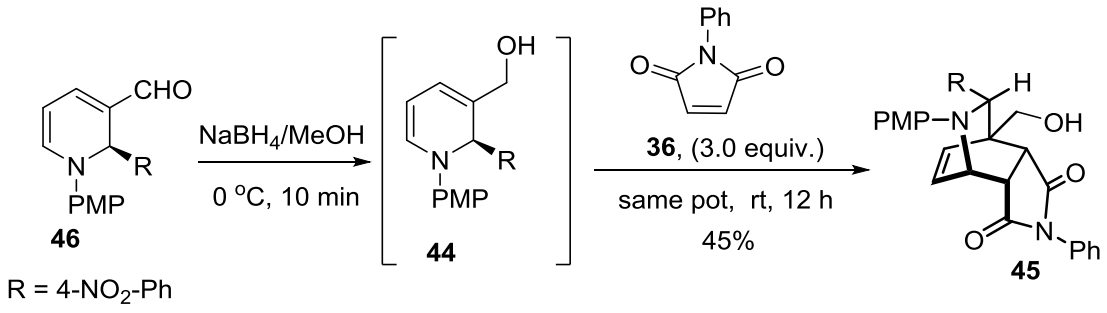


Table 5.1 Initial experimental failures for the diastereoselective [4+2] cycloaddition

S.No	equiv of **36**	condition 2	additive	yield of **47**
1	1	DMSO, rt, 24h	-	-
2	2	DCM, rt, 24h	-	-
3	2	Toluene, rt, 24h	AcOH	**46** decomposed
4	2	CH_3CN, rt, 24h	AgOTf	**46** decomposed
5	2	MeOH, rt, 24h	$In(OTf)_3$	-
6	3	THF, rt, 24h	-	-
7	3	Xylene, 110 °C, 4 h	-	-

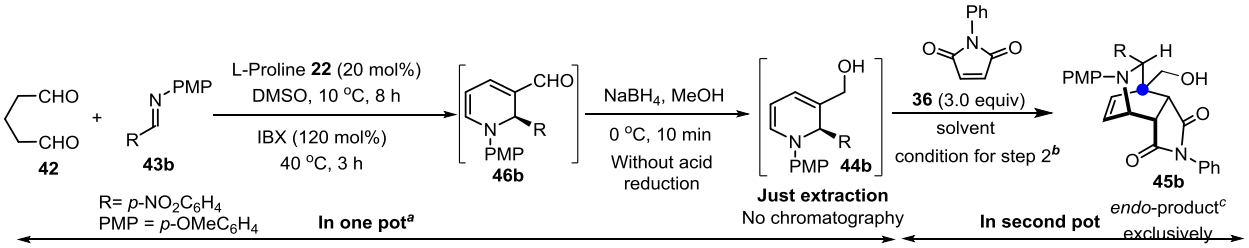


Scheme 5.12 Diastereoselective [4+2] cycloaddition of chiral 1,2-DHPs

Having learned these failures, it was clear that the presence of formyl group at C3 posisiton of **46** is making the ring much more electron deficient diene and hence it was not undergoing the normal electron-demand Diels-Alder reaction (NEDDA) with already electron deficient dienophile **36**. Therefore, we plan to reduce –CHO group to corresponding alcohol before executing [4+2] D-A recation with suitable dienophile. Therefore, -CHO group of dihydropyridine **46** was reduced into corresponding alcohol by $NaBH_4$ in methanol. The resulting alcohol/dienamine **44** was used further without isolation for D-A reaction with N-Phenyl maleimide **36** (3.0 equiv) in the same pot. Pleasingly, the diastereoselective Diels-Alder reaction gave isoquinuclidines **45** without any additive or catalyst in 45% yield as shown in **Scheme 5.12**.

Having initial success in hand, we tried to make this reaction successful in one/two pot from glutaraldehyde and imine as enantio- and diastereoselective synthesis of isoquinuclidines. In oder to make this idea worth, we started with imine and glutaraldehyde and find the best reaction condition as two pot procedure as shown in Table 5.2. Initially, we obtained the poor yield when the process of [4+2] annulation between glutaraldehdye and imine followed by D-A reaction of *in situ* generated dienamine with **36** was carried out in DMSO as one-pot operation. However, was used as solvent for both steps *i.e.* (entry 1, **Table 5.2**).

Table 5.2 Standardization of the reaction condition (**45b**)



S.No	equiv of **36**	condition for step 2[b]	yield of **45b**	dr[d]	er[e]
1	1.5	DMSO, rt, 5h	21	>50:1	90:10
2	3	MeOH, rt, 8h	45	>50:1	90:10
3	2	CH_3CN, 10 °C, 8h	30	>50:1	94:6
4	2	Toluene, rt, 12h	68	>25:1	90:10
5	**3**	**CH_2Cl_2, rt, 12h**	**81**	**>50:1**	**94:6**
6	3	THF, rt, 24 h	52	>50:1	94:6
7	3	Dioxane	55	>50:1	94:6

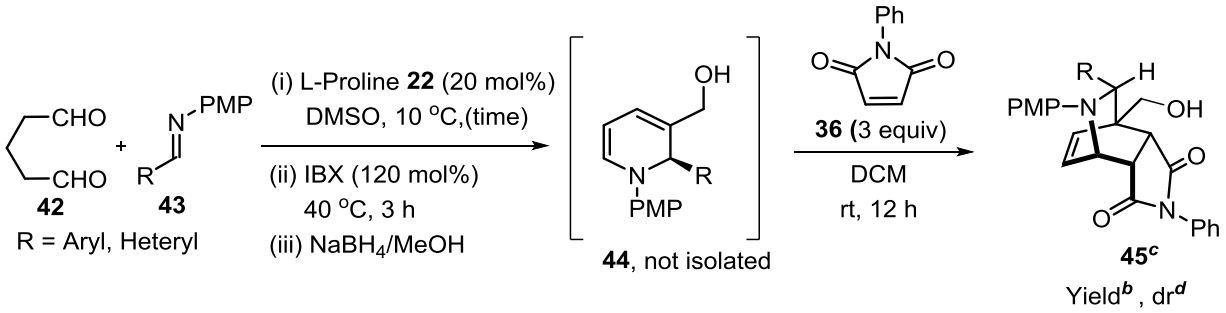
Unless other wise stated in condition 1, [a] imine was used (0.3 mmol), aqueous glutaraldehyde (0.9 mmol), L-Proline (20 mol%), DMSO (3 mL), IBX (120 mol%), MeOH (3 mL). Condition 2, [b] Solvent was used 3 mL, and the reaction was carried out at rt in a stoppered vesscle. [c] Yields are after isolation using silica gell column chromatography with respect to preformed imine used in the reaction. [d] Only endo product was obtained and dr was determined by ^{1}H NMR. [e] Enantioselectivity was determined using chiral stationary phase HPLC chromatography.

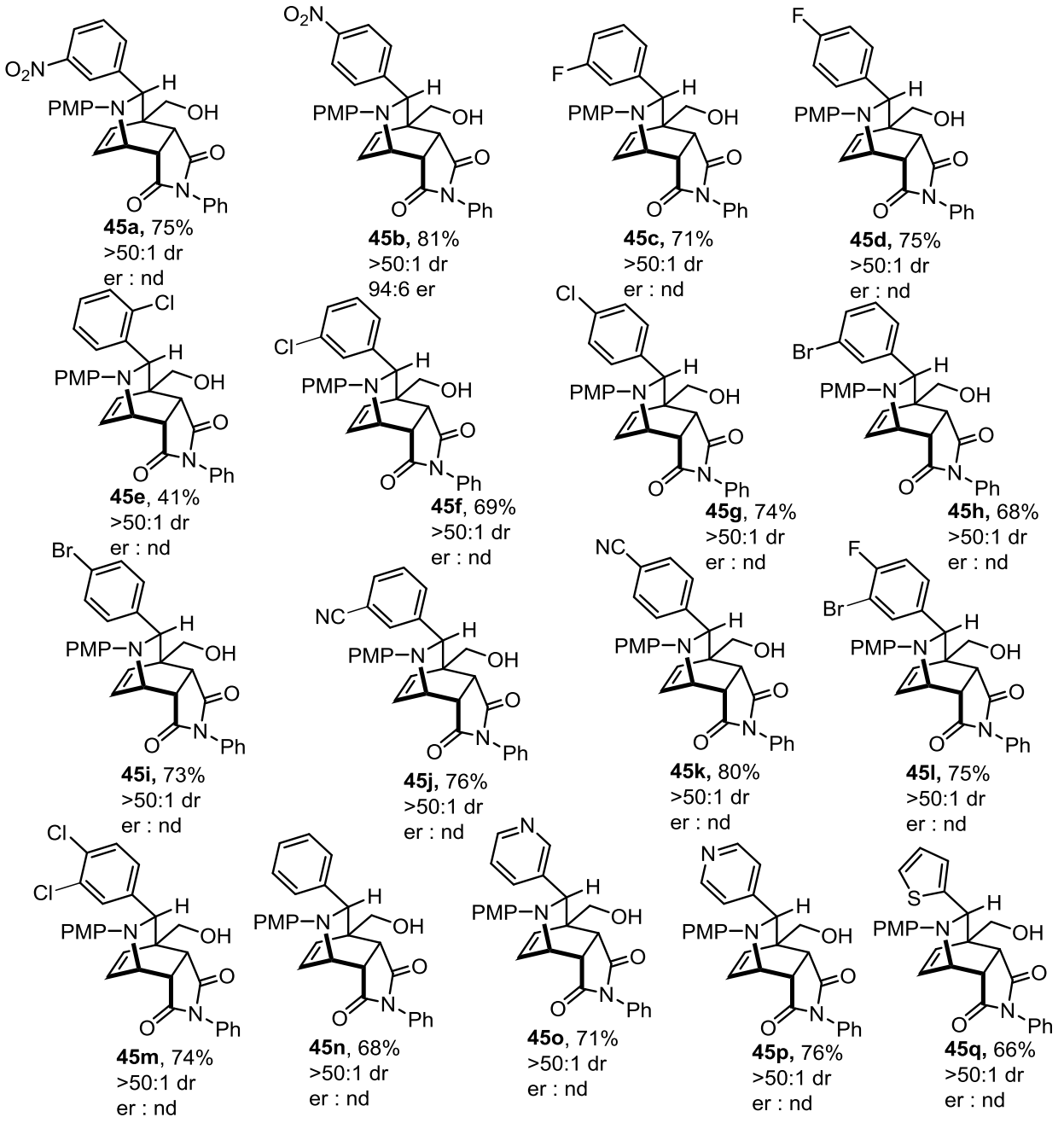
The reaction yields was further improved when step 1 (Direct Mannich/cyclization/IBX-oxidation/$NaBH_4$ reduction) was carried out as our standard procedure in DMSO, followed by step 2 (D-A reaction with **36**) was carried out by changing the reaction solvent at II-step without isolation at intermediate dienamine **44** stage with high selectivity (entries 2-4, **Table 5.2**). Pleasingly, we obtained high yield and excellent enantio- (94:6 er) and diastereoselelctivty (>25:1), when the reaction of in situ generated **44** with **36** was carried out in (enrty 5, **Table 5.2**). Any further change in solvent and reaction conditions could not provide better yields (entry 4, T**able 5.2**).

With the optimized reaction condition in hand, substrate scope was further explored with respect to various preformed imines. The reaction produced very good yields when the aryl ring has the electron withdrawing substrate at *meta*- and *para*-positions. (**45a – 45n** except **45e**, **Table 5.3**) However, this two pot protocol did work with poor yields when the aryl group was *ortho*-substituted (**45e, Table 5.3**), may be because of steric crowding.

The reaction proceeded well when used hetero-arylimines and produced the corresponding [4+2] Diels-Alder product of isoquinuclidines (**45o, 45p, 45q, Table 5.3**) in good yields and excellent diastereomeric ratio. All the compounds were characterized by ^{1}H NMR, ^{13}C NMR, and the absolute stereochemistry was confirmed by X-ray crystallographic study as shown in **Figure 5.4**.

Table 5.3 Substrate scope of the reaction for the synthesis of isoquinuclidines (**45**).





[a]Unless otherwise stated, (i) imine (0.3 mmol), aqueous glutaraldehyde (0.9 mmol), L-Proline (20 mol %), DMSO (3.0 mL), IBX (120 mol %), $NaBH_4$ (portionwise), (ii) MeOH (3.0 mL), 36 (3.0 equiv.), rt, 12 h. [b]Yields are after chromatographic purification. [c]Only *endo*-product was obtained. [d]dr was determined by ^1H NMR. (nd = Not determined).

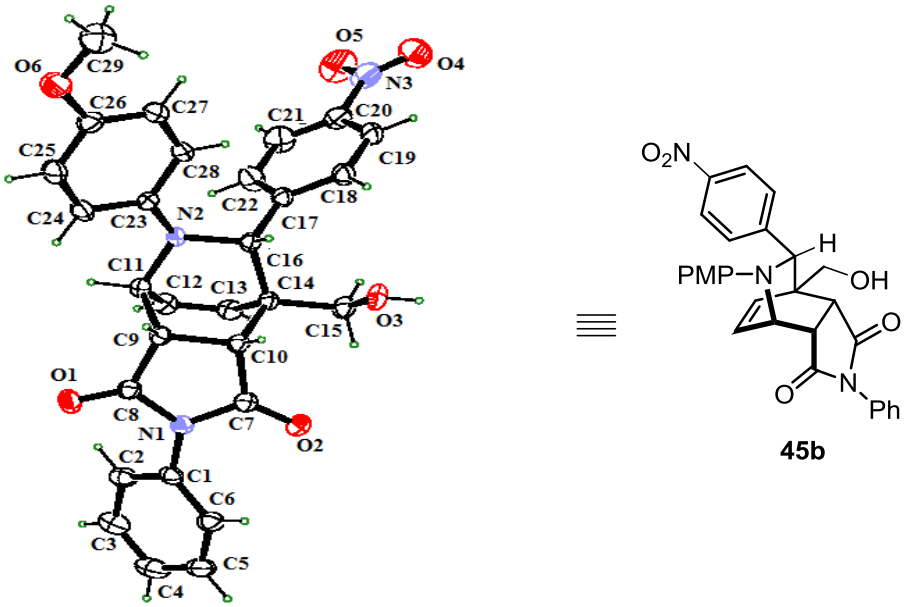


Figure 5.4 Single crystal X-ray diagram of isoquinuclidines **45b**

5.4 Conclusion:

In the conclusion, we developed a simple, innovative and highly practical approach for the enantio-, and diastereoselective synthesis of isoquinuclidines **45** from the easily available glutaraldehyde and imine in a two-pot domino fashion. The overall reaction proceeded through *in situ* formation of dienamine followed by [4+2] Diels-Alder reaction without any isolation at the intermediate stage. High level of enantio selectivity (94:6 er) and diastereoselectivity >25:1 dr) is obtained for *endo*-product **45b** and the determination of enantioselectivity of other compounds through HPLC using chiral stationary phase is under progress.

5.5 General Experimental Methods:

All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on SiO_2 gel F-254 plates. The normal column chromatography was performed on silica gel (100-200 mesh) and Flash column chromatography was performed on silica gel (230-400 meshes) using the mixture of Hexane-EtOAc as eluting solvent. All reagents were of analytical grade and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution and spectral data were reported in ppm relative to tetramethylsilane (TMS) as internal standard. High resolution mass spectra were recorded using quadrupleelectro spray ionization (ESI) technique.

Specific rotation was measured through RUDOLPH Polari meter. Melting point was determined by EZ–Melt, Automated Melting Point Apparatus (SRS Stanford Research System, SIN: 78476).

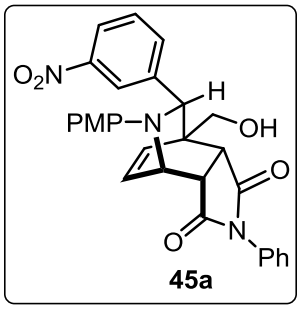
5.6 General procedure for the stereo selective synthesis of isoquinuclidines via [4+2] Diels – Alder reaction:

To the imine **43** (0.3 mmol), in DMSO (3 mL) was added glutaraldehdye **42** (0.36 mL, 0.9 mmol), and L-Proline **22** (7 mg, 20 mol%) at 10 ^{o}C and stirred the reaction mixture until the imine is consumed which was monitored by TLC. Then IBX (92 mg, 120 mol%) was added and stirred the reaction at 40 ^{o}C for 3 hours which was monitored by TLC. Once the intermediate enamine is totally converted int its corresponding 1,2-DHP **46**, followed by $NaBH_4$ addition (portiowise) at 0 ^{o}C until the 1,2-DHP **46** consumed completely as indicated by the dark red color of the solution turned into pale yellow (reduction time is approximately 5–10 min). Then to the reaction mixture was added ethyl acetate (10 mL) and stirred for 10 minutes. Then saturated $NaHCO_3$ solution (10 mL) was added slowly and stirred for 5 minutes. The organic layer was separated and the aqueous solution was extracted with ethyl acetate (2 x 10 mL) and combined organic extracts were washed with brine once, dried over anhydrous Na_2SO_4 and concentrated in vacuum after filtration. The crude 1,2-DHP alcohol **44** was directly used for the above said Diels–Alder reaction without further purification.

To the crude DHP alcohol **44** (0.25 mmol) in 10 ml round bottomed flask, dichloromethane (3 mL) was added followed by N-phenyl malimide **36** (0.75 mmol, 3 equiv) at room temperature. Then the flask was stoppered and the reaction was stirred for 12 hours at room temperature which was monitored by TLC. Once the DHP alcohol **44** was consumed completely, the reaction mixture was evaporated through rotavapour and the crude residue was purified by column chromatography on silica gel (Hexane: EtOAc) to afford isoquinuclidines **45** high yields (up to 81%).

5.7 Characterization data:

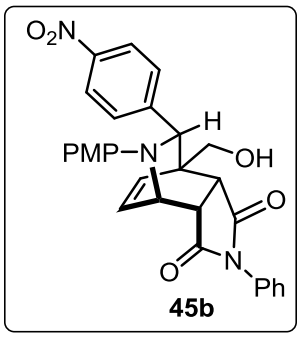
(3a*S*,4*S*,7*S*,7a*R*)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-8-(3-nitrophenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45a)



45a

Pale yellow solid, (75% yield), Melting Point = 208 – 211 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (t, *J* = 5.8 Hz, *J* = 5.9 Hz, 1H), 3.47 (d, *J* = 8.2 Hz, 1H), 3.53 (dd, *J* = 12.1, *J* = 6.0 Hz, 1H), 3.72 (s, 3H), 3.76 (dd, *J* = 8.2 Hz, *J* = 3.9 Hz, 1H), 4.27 (dd, *J* = 12.1 Hz, *J* = 5.9 Hz, 1H), 4.59 (s, 1H), 5.23 – 5.26 (m, 1H), 5.70 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 9.3 Hz, 2H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.88 – 6.91 (m, 1H), 7.17 – 7.19 (m, 2H), 7.39 – 7.42 (m, 1H), 7.45 – 7.53 (m, 3H), 7.83 (d, *J* = 7.6 Hz, 1H), 8.13 – 8.16 (m, 1H), 8.28 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.63, 42.77, 48.04, 49.42, 55.56, 60.11, 64.19, 115.00 (2C), 115.21 (2C), 122.92, 123.44, 126.27 (2C), 128.89, 129.06, 129.17 (2C), 131.10, 131.34, 133.27, 134.85, 140.04, 142.43, 148.32, 152.84, 175.67, 176.32; IR (KBr)/cm^{-1} 3495, 3078, 2932, 1699, 1605, 1512, 1358, 1203, 1041, 802; HRMS (ESI): Calcd for $C_{29}H_{25}N_3O_6$ (MH^+) 512.1821; Found: 512.1823. $[\alpha]_D^{25}$ = – 98 (*c* 0.1, CH_2Cl_2).

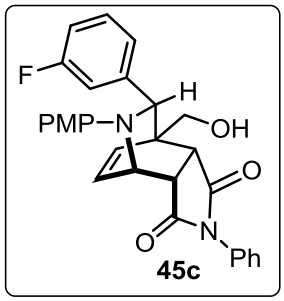
(3a*S*,4*S*,7*S*,7a*R*)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-8-(4-nitrophenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45b)



45b

Pale yellow solid, (81% yield), Melting Point = 219 – 221 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (t, *J* = 5.6 Hz, *J* = 5.8 Hz, 1H), 3.47 (d, *J* = 8.1 Hz, 1H), 3.54 (dd, *J* = 11.5, *J* = 6.1 Hz, 1H), 3.71 (s, 3H), 3.75 – 3.78 (m, 1H), 4.26 (dd, *J* = 12.2 Hz, *J* = 4.7 Hz, 1H), 4.57 (s, 1H), 5.22 – 5.25 (m, 1H), 5.69 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 9.2 Hz, 2H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.85 – 6.88 (m, 1H), 7.16 – 7.18 (m, 2H), 7.39 – 7.41 (m, 1H), 7.45 – 7.49 (m, 2H), 7.63 (d, *J* = 8.4 Hz, 2H), 8.17 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.77, 42.84, 48.19, 49.30, 55.62, 60.26, 64.61, 115.07 (2C), 115.11 (2C), 123.40 (2C), 126.29 (2C), 128.96, 129.22 (2C), 129.56 (2C), 131.20, 131.34, 133.25, 140.04, 147.65 (2C), 152.88, 175.62, 176.26; IR (KBr)/cm^{-1} 3448, 2932, 2854, 1705, 1597, 1358, 1250, 1188, 1034, 810, 733; HRMS (ESI): Calcd for $C_{29}H_{25}N_3O_6$ (MH^+) 512.1821; Found: 512.1822. $[\alpha]_D^{25}$ = – 58 (*c* 0.3, CH_2Cl_2).

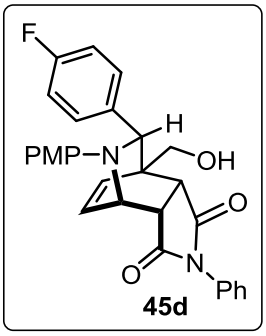
(3a*S*,4*S*,7*S*,7a*R*)-8-(3-fluorophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45c)



45c

Pale brown solid, (71% yield), Melting Point = 178 – 181 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (t, *J* = 5.7 Hz, *J* = 6.0 Hz, 1H), 3.42 (d, *J* = 8.2 Hz, 1H), 3.66 (dd, *J* = 12.0, *J* = 6.1 Hz, 1H), 3.72 - 3.76 (m, 4H), 4.16 (dd, *J* = 12.0 Hz, *J* = 5.5 Hz, 1H), 4.42 (s, 1H), 5.19 – 5.22 (m, 1H), 5.74 (d, *J* = 8.1 Hz, 1H), 6.73 (d, *J* = 9.3 Hz, 2H), 6.78 (d, *J* = 9.3 Hz, 2H), 6.80 – 6.84 (m, 1H), 6.94 – 6.99 (m, 1H), 7.11 (d, *J* = 9.8 Hz, 1H), 7.17 – 7.19 (m, 2H), 7.24 – 7.26 (m, 1H), 7.28 – 7.32 (m, 1H), 7.38 – 7.42 (m, 1H), 7.45 – 7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.92, 42.81, 48.09, 49.14, 55.59, 60.49, 64.84, 114.96 (2C), 124.27, 124.30, 126.30 (2C), 128.84, 129.15 (2C), 129.51, 129.59, 131.42, 131.70, 132.70, 140.51, 142.84, 142.90, 152.96, 161.58, 164.03, 175.86, 17.61; IR (KBr)/cm^{-1} 3418, 2924, 2847, 1605, 1520, 1458, 1342, 1250, 1188, 1034; HRMS (ESI): Calcd for $C_{29}H_{25}FN_2O_4$ (MH^+) 485.1876; Found: 485.1875. $[\alpha]_D^{25}$ = – 29 (*c* 0.6, CH_2Cl_2).

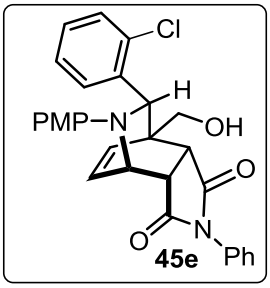
(3a*S*,4*S*,7*S*,7a*R*)-8-(4-fluorophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45d)



45d

White solid, (75% yield), Melting Point = 196 – 198 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (t, *J* = 6.3 Hz, *J* = 6.2 Hz, 1H), 3.41 (d, *J* = 8.2 Hz, 1H), 3.64 (dd, *J* = 12.3, *J* = 5.5 Hz, 1H), 3.72 – 3.76 (m, 4H), 4.14 (dd, *J* = 11.1 Hz, *J* = 3.6 Hz, 1H), 4.42 (s, 1H), 5.19 – 5.21 (m, 1H), 5.72 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 9.3 Hz, 2H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.79 – 6.83 (m, 1H), 6.99 (t, *J* = 8.7 Hz, *J* = 8.7 Hz, 2H), 7.17 – 7.19 (m, 2H), 7.37 – 7.42 (m, 3H), 7.45 – 7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.94, 42.87, 48.15, 49.14, 55.60, 60.59, 64.68, 111.94 (3C), 115.15, 126.30 (2C), 128.86, 129.16 (2C), 130.06, 130.14, 131.42, 131.74, 132.70, 135.54, 135.57, 140.60, 152.49, 161.14, 163.59, 175.90, 176.70; IR (KBr)/cm^{-1} 3458, 3063, 2939, 2847, 1705, 1597, 1504, 1458, 1381, 1242, 1041, 810; HRMS (ESI): Calcd for $C_{29}H_{25}FN_2O_4$ (MH^+) 485.1876; Found: 485.1874. $[\alpha]_D^{25}$ = – 25 (*c* 0.4, CH_2Cl_2).

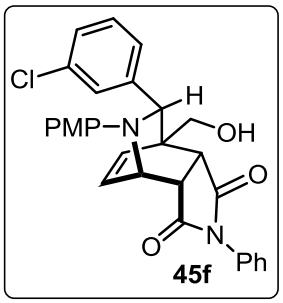
(3a*S*,4*S*,7*S*,7a*R*)-8-(2-chlorophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45e)



45e

Pale brown solid, (41% yield), Melting Point = 168 – 171 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.34 – 3.37 (m, 1H), 3.44 (d, *J* = 8.1 Hz, 1H), 3.67 – 3.70 (m, 2H), 3.72 (s, 3H), 3.75 – 3.82 (m, 2H), 4.03 (dd, *J* = 12.7 Hz, *J* = 5.7 Hz, 1H), 4.80 (s, 1H), 5.19 – 5.21 (m, 1H), 6.20 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 9.3 Hz, 2H), 6.80 (d, *J* = 9.3 Hz, 2H), 6.85 – 6.88 (m, 3H), 7.13 – 7.23 (m, 5H), 7.33 – 7.42 (m, 6H), 7.45 – 7.50 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.77, 45.29, 48.71, 50.12, 55.59, 60.82, 62.63, 115.04, 115.30, 126.05, 126.35, 127.15, 127.97, 128.99, 129.14, 129.18, 129.21, 129.26, 130.73, 132.34, 132.70, 133.98, 134.19, 137.22, 139.98, 152.86, 169.51, 175.71, 177.74; IR (KBr)/cm^{-1} 3448, 2932, 2854, 1705, 1597, 1512, 1381, 1250; HRMS (ESI): Calcd for $C_{29}H_{25}ClN_2O_4$ (MH^+) 501.1581; Found: 501.1583. $[\alpha]_D^{25}$ = – 15 (*c* 0.1, CH_2Cl_2).

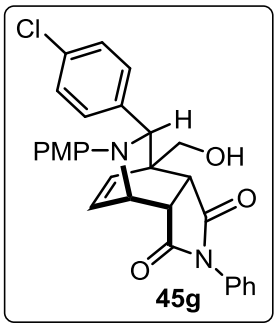
(3a*S*,4*S*,7*S*,7a*R*)-8-(3-chlorophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45f)



45f

Pale brown solid, (69% yield), Melting Point = 183 – 186^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.56 (t, *J* = 5.5 Hz, *J* = 5.5 Hz, 1H), 3.41 (d, *J* = 8.1 Hz, 1H), 3.63 (dd, *J* = 12.1, *J* = 6.0 Hz, 1H), 4.41 (s, 3H), 5.19 – 5.21 (m, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 9.3 Hz, 2H), 6.79 (d, *J* = 9.3 Hz, 2H), 6.81 – 6.84 (m, 1H), 7.16 – 7.19 (m, 2H), 7.25 – 7.26 (m, 2H), 7.34 – 7.42 (m, 3H), 7.44 – 7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.86, 42.76, 48.06, 49.13, 55.59, 60.43, 64.83, 114.95 (2C), 114.98 (2C), 126.28, 126.89, 128.00, 128.48, 128.84, 19.14, 129.14 (2C), 129.37, 131.39, 131.60, 132.75, 134.20, 140.47, 142.26, 152.57, 175.84, 176.56; IR (KBr)/cm^{-1} 3495, 3063, 2924, 2839, 1697, 1589, 1504, 1389, 1250, 1196, 1041; HRMS (ESI): Calcd for $C_{29}H_{25}ClN_2O_4$ (MH^+) 501.1581; Found: 501.1583. $[\alpha]_D^{25}$ = – 70 (*c* 0.1, CH_2Cl_2).

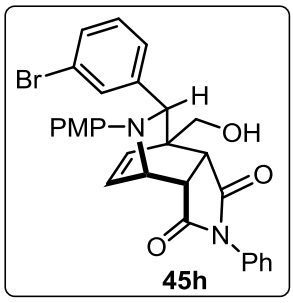
(3a*S*,4*S*,7*S*,7a*R*)-8-(4-chlorophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45g)



45g

White solid, (74% yield), Melting Point = 203 – 206 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 1H), 3.41 (d, *J* = 8.1 Hz, 1H), 3.62 (d, *J* = 11.9 Hz, 1H), 3.72 – 3.75 (m, 4H), 4.16 (d, *J* = 11.9 Hz, 1H), 4.41 (s, 1H), 5.18 – 5.21 (m, 1H), 5.70 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 9.3 Hz, 2H), 6.78 (d, *J* = 9.4 Hz, 2H), 6.81 – 6.83 (m, 1H), 7.16 – 7.18 (m, 2H), 7.28 (d, *J* = 8.7 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 7.39 – 7.42 (m, 1H), 7.44 – 7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.90, 42.92, 48.17, 49.20, 55.67, 60.48, 64.72, 115.03 (2C), 126.37 (2C), 128.42 (2C), 128.93, 129.23 (2C), 130.01 (2C), 131.49, 131.72 (2C), 132.81 (2C), 133.57, 138.56, 140.59, 152.59, 175.96, 176.71; IR (KBr)/cm^{-1} 3464, 2924, 1897, 1497, 1381, 1250, 1188, 1034, 810; HRMS (ESI): Calcd for $C_{29}H_{25}ClN_2O_4$ (MH^+) 501.1581; Found: 501.1582. $[\alpha]_D^{25}$ = – 44 (*c* 0.8, CH_2Cl_2).

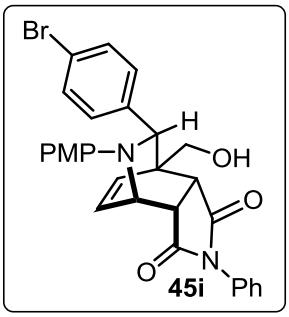
(3a*S*,4*S*,7*S*,7a*R*)-8-(3-bromophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45h)



45h

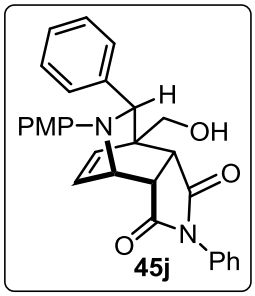
White solid, (68% yield), Melting Point = 134 – 136.5 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (t, *J* = 5.9 Hz, *J* = 5.9 Hz, 1H), 3.41 (d, *J* = 8.1 Hz, 1H), 3.64 (dd, *J* = 12.1, *J* = 6.0 Hz, 1H), 3.72 (s, 3H), 3.73 – 3.75 (m, 1H), 4.17 (dd, *J* = 12.0, *J* = 5.2 Hz, 1H), 4.40 (s, 1H), 5.19 – 5.21 (m, 1H), 5.73 (d, *J* = 8.2 Hz, 1H), 6.72 (d, *J* = 9.3 Hz, 2H), 6.79 (d, *J* = 9.3 Hz, 2H), 6.81 – 6.84 (m, 1H), 7.17 – 7.21 (m, 3H), 7.38 – 7.42 (m, 3H), 7.45 – 7.49 (m, 2H), 7.53 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.84, 42.74, 48.07, 49.13, 55.59, 60.38, 64.77, 114.16, 114.49 (2C), 120.85, 122.49, 126.28 (2C), 127.36, 128.83, 129.13 (2C), 129.67, 130.91, 131.34, 131.38, 131.58, 132.74, 140.46, 142.52, 152.57, 175.83, 176.54; IR (KBr)/cm^{-1} 3458, 3063, 2924, 2847, 1795, 1597, 1504, 1381, 1250, 1188, 1041, 810; HRMS (ESI): Calcd for $C_{29}H_{25}BrN_2O_4$ (MH^+) 545.1076; Found: 545.1078. $[\alpha]_D^{25}$ = – 63 (*c* 0.2, CH_2Cl_2).

(3a*S*,4*S*,7*S*,7a*R*)-8-(4-bromophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45i)



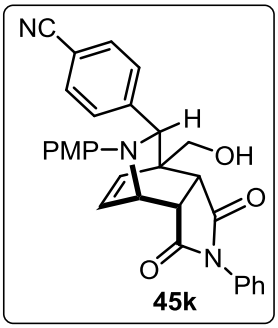
White solid, (73% yield), Melting Point = 162 – 165 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.49 (t, *J* = 6.0 Hz, *J* = 5.9 Hz, 1H), 3.41 (d, *J* = 8.1 Hz, 1H), 3.63 (dd, *J* = 12.1, *J* = 6.1 Hz, 1H), 3.72 (s, 3H), 3.72 – 3.75 (m, 1H), 4.16 (dd, *J* = 11.9, *J* = 5.2 Hz, 1H), 4.40 (s, 1H), 5.19 – 5.21 (m, 1H), 5.70 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 9.4 Hz, 2H), 6.78 (d, *J* = 9.4 Hz, 2H), 6.79 – 6.83 (m, 1H), 7.16 – 7.18 (m, 2H), 7.30 (d, J = 8.3 Hz, 2H), 7.40 – 7.42 (m, 2H), 7.44 – 7.48 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.80, 42.81, 48.01, 49.10, 55.57, 60.38, 64.68, 114.10, 114.93 (2C), 121.05, 121.70, 126.26 (2C), 128.83, 129.13 (2C), 130.28 (2C), 131.26 (2C), 131.38, 131.59, 132.73, 138.99, 140.46, 152.50, 175.84, 176.57; IR (KBr)/cm^{-1} 3456, 2932, 1697, 1504, 1381, 1250, 1188, 1034, 810; HRMS (ESI): Calcd for $C_{29}H_{25}BrN_2O_4$ (MH^+) 545.1076; Found: 545.1079. $[\alpha]_D^{25}$ = – 116 (*c* 0.3, CH_2Cl_2).

3-((3a*S*,4*S*,7*S*,7a*R*)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-(epiminomethano)isoindol-8-yl)benzonitrile: (45j)



White solid, (76% yield), MP = 173 – 175 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (t, *J* = 5.9 Hz, *J* = 6.0 Hz, 1H), 3.45 (d, *J* = 8.1 Hz, 1H), 3.52 (dd, *J* = 12.0, *J* = 6.0 Hz, 1H), 3.72 (s, 3H), 3.74 – 3.76 (m, 1H), 4.24 (dd, *J* = 2.1 Hz, *J* = 5.6 Hz, 1H), 4.50 (s, 1H), 5.21 – 5.24 (m, 1H), 5.69 (d, *J* = 8.2 Hz, 1H), 6.69 (d, *J* = 9.3 Hz, 2H), 6.79 (d, *J* = 9.3 Hz, 2H), 6.80 – 6.88 (m, 1H), 7.16 – 7.19 (m, 2H), 7.40 – 7.49 (m, 4H), 7.56 – 7.59 (m, 1H), 7.72 – 7.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.55, 42.73, 47.97, 49.30, 55.54, 59.97, 64.13, 114.95 (2C), 115.09 (2C), 118.87, 121.14, 126.25 (2C), 128.82, 128.87, 129.11 (2C), 131.20, 131.32, 131.43, 132.14, 133.05, 133.19, 140.03, 141,64, 152.72, 175.67, 176.29; IR (KBr)/cm^{-1} 3495, 3063, 2932, 2847, 2230, 1697, 1597, 1504, 1389, 1196, 1034; HRMS (ESI): Calcd for $C_{30}H_{25}N_3O_4$ (MH^+) 492.1923; Found: 492.1921. $[\alpha]_D^{25}$ = – 80 (*c* 0.1, CH_2Cl_2).

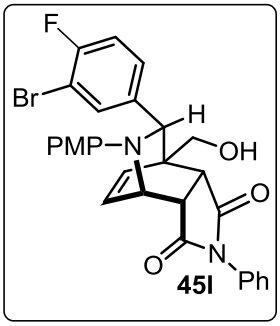
4-((3a*S*,4*S*,7*S*,7a*R*)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-1,3-dioxo-2-phenyl-2,3,3a,4,7,7a-hexahydro-1*H*-4,7-(epiminomethano)isoindol-8-yl)benzonitrile: (45k)



45k

White solid, (80% yield), MP = 240 – 243 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.52 (t, *J* = 6.0 Hz, *J* = 6.0 Hz, 1H), 3.44 (d, *J* = 8.2 Hz, 1H), 3.53 (dd, *J* = 12.2, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 3.73 – 3.76 (m, 1H), 4.22 (dd, *J* = 12.2, *J* = 5.6 Hz, 1H), 4.51 (s, 1H), 5.21 – 5.23 (m, 1H), 5.68 (d, *J* = 8.1 Hz, 1H), 6.67 (d, *J* = 9.3 Hz, 2H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.82 – 6.86 (m, 1H), 7.17 (d, J = 7.1 Hz, 2H), 7.38 – 7.42 (m, 1H), 7.44 – 7.48 (m, 2H), 7.55 – 7.62 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.62, 42.75, 48.06, 49.18, 55.54, 60.04, 64.63, 111.50, 114.14, 114.98 (2C), 118.71, 121.13, 126.23 (2C), 128.86, 129.12 (2C), 129.37, 131.23, 131.30, 131.66, 131.92 (2C), 132.99 (2C), 140.07, 145.60, 152.69, 175.66, 176.28; IR (KBr)/cm^{-1} 3484, 3070, 2932, 2230, 1705, 1597, 1381, 1257, 1188, 1034; HRMS (ESI): Calcd for $C_{30}H_{25}N_3O_4$ (MH^+) 492.1923; Found: 492.1920. $[\alpha]_D^{25}$ = – 150 (*c* 0.2, CH_2Cl_2).

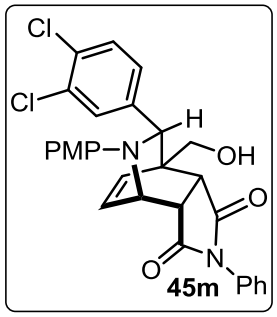
(3a*S*,4*S*,7*S*,7a*R*)-8-(3-bromo-4-fluorophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45l)



45l

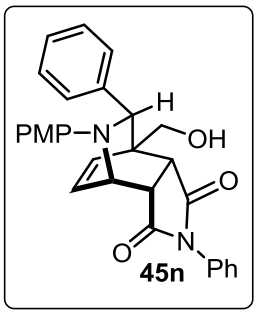
White solid, (75% yield), Melting Point = 142 – 145 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.43 (t, *J* = 6.0 Hz, *J* = 6.1 Hz, 1H), 3.41 (d, *J* = 8.1 Hz, 1H), 3.61 (dd, *J* = 12.1, *J* = 6.2 Hz, 1H), 3.72 – 3.75 (m, 4H), 4.21 (dd, *J* = 12.1, *J* = 5.6 Hz, 1H), 4.40 (s, 1H), 5.18 – 5.21 (m, 1H), 5.71 (d, *J* = 8.1 Hz, 1H), 6.71 (d, *J* = 9.2 Hz, 2H), 6.79 (d, *J* = 9.3 Hz, 2H), 6.81 – 6.85 (m, 1H), 7.07 (t, *J* = 8.4 Hz, 8.3 Hz, 1H), 7.16 – 7.18 (m, 2H), 7.37 – 7.42 (m, 2H), 7.45 – 7.48 (m, 2H), 7.58 – 7.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.68, 42.74, 48.05, 49.19, 55.59, 60.24, 64.05, 114.97 (2C), 115.07 (2C), 115.92, 116.14, 126.27 (2C), 128.87, 129.12, 129.15 (2C), 131.36, 131.44, 132.88, 133.27, 137.41, 137.44, 140.30, 152.69, 175.77, 176.47; IR (KBr)/cm^{-1} 3458, 2924, 1795, 1504, 1497, 1381, 1250, 1188, 1034; HRMS (ESI): Calcd for $C_{29}H_{24}BrFN_2O_4$ (MH^+) 563.0981; Found: 563.0983. $[\alpha]_D^{25}$ = – 40 (*c* 0.6, CH_2Cl_2).

(3a*S*,4*S*,7*S*,7a*R*)-8-(3,4-dichlorophenyl)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45m)



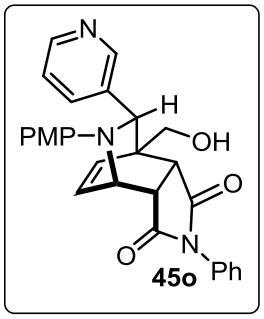
White solid, (74% yield), Melting Point = 193 – 195 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (t, *J* = 6.0 Hz, *J* = 6.0 Hz, 1H), 3.42 (d, *J* = 8.2 Hz, 1H), 3.58 – 3.63 (m, 1H), 3.73 – 3.75 (m, 4H), 4.22 (dd, *J* = 12.1, *J* = 6.1 Hz, 1H), 4.40 (s, 1H), 5.18 – 5.21 (m, 1H), 5.71 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 9.3 Hz, 2H), 6.79 (d, *J* = 9.2 Hz, 2H), 6.81 – 6.85 (m, 1H), 7.16 – 7.18 (m, 2H), 7.30 – 7.32 (m, 1H), 7.38 – 7.42 (m, 2H), 7.45 – 7.50 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.68, 42.74, 48.05, 49.18, 55.60, 60.23, 64.18, 114.99 (2C), 115.07 (2C), 126.27 (2C), 128.02, 128.88, 129.17 (2C), 130.08, 130.31, 131.35, 131.38, 131.74, 132.40, 132.95, 140.24, 140.45, 152.73, 175.74, 176.42; IR (KBr)/cm^{-1} 3456, 2923, 2840, 1606, 1520, 1458, 1343, 1251, 1189, 1036; HRMS (ESI): Calcd for $C_{29}H_{24}Cl_2N_2O_4$ (MH^+) 535.1191; Found: 535.1193; $[\alpha]_D^{25}$ = – 66 (*c* 0.4, CH_2Cl_2).

(3a*S*,4*S*,7*S*,7a*R*)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2,8-diphenyl-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45n)



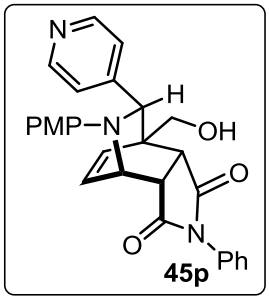
White solid, (68% yield), MP = 200 – 203 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.48 (t, *J* = 6.4 Hz, *J* = 6.4 Hz, 1H), 3.42 (d, *J* = 8.2 Hz, 1H), 3.67 – 3.72 (m, 4H), 3.76 (dd, *J* = 8.1, *J* = 3.9 Hz, 1H), 4.10 (dd, *J* = 12.1, *J* = 5.8 Hz, 1H), 4.41 (s, 1H), 5.20 – 5.23 (m, 1H), 5.75 (d, *J* = 8.1 Hz, 1H), 6.72 – 6.78 (m, 4H), 6.80 – 6.83 (m, 1H), 7.17 – 7.19 (m, 2H), 7.27 – 7.33 (m, 3H), 7.38 – 7.42 (m, 3H), 7.45 – 7.48 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 42.17, 42.88, 48.19, 49.09, 55.60, 60.81, 65.56, 114.86 (2C), 114.92 (2C), 126.31 (2C), 127.77, 128.18 (2C), 128.56 (2C), 128.82, 129.14 (2C), 131.45, 131.92, 132.55, 139.94, 140.80, 152.6, 175.98, 176.81; IR (KBr)/cm^{-1} 3425, 3055, 2924, 2854, 1697, 1597, 1504, 1381, 1250, 1188, 1034, 725; HRMS (ESI): Calcd for $C_{29}H_{26}N_2O_4$ (MH^+) 467.1971; Found: 467.1973; $[\alpha]_D^{25}$ = – 50 (*c* 0.1, CH_2Cl_2).

(3a*S*,4*S*,7*S*,7a*R*)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-8-(pyridin-3-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45o)



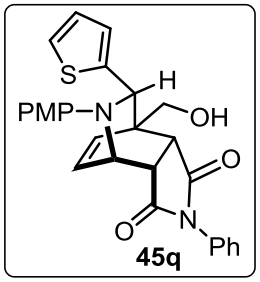
Brown solid, (71% yield), MP = 143 – 145 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.48 (d, *J* = 8.1 Hz, 1H), 3.56 (d, *J* = 11.9 Hz, 1H), 3.71 – 3.78 (m, 5H), 4.26 (d, *J* = 11.9 Hz, 1H), 4.54 (s, 1H), 5.20 – 5.23 (m, 1H), 5.73 (d, *J* = 8.1 Hz, 1H), 6.72 (d, *J* = 9.3 Hz, 2H), 6.78 (d, *J* = 9.3 Hz, 2H), 6.83 – 6.87 (m, 1H), 7.16 – 7.19 (m, 2H), 7.22 – 7.24 (m, 1H), 7.38 – 7.42 (m, 1H), 7.45 – 7.49 (m, 2H), 7.73 (d, *J* = 7.9 Hz, 1H), 8.52 – 8.53 (m, 1H), 8.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.45, 42.71, 48.00, 49.47, 55.57, 59.63, 62.51, 114.96 (2C), 115.15 (2C), 123.35, 126.30, 128.80, 129.12 (2C), 131.45, 131.57, 131.61, 132.88, 135.91, 136.59, 140.18, 148.68, 149.91, 152.67, 175.80, 176.22; IR (KBr)/cm^{-1} 3441, 3063, 2924, 2847, 1796, 1597, 1504, 1381; HRMS (ESI): Calcd for $C_{28}H_{25}N_3O_4$ (MH^+) 468.1923; Found: 468.1925. $[\alpha]_D^{25}$ = – 33 (*c* 0.3, CH_2Cl_2).

(3a*S*,4*S*,7*S*,7a*R*)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-8-(pyridin-4-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45p)



Brown solid, (76% yield), MP = 158 – 161 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (d, *J* = 8.1 Hz, 1H), 3.59 (d, *J* = 12.1 Hz, 1H), 3.72 (s, 3H), 3.76 (dd, *J* = 8.2, *J* = 3.9 Hz, 1H), 4.25 (d, *J* = 12.1 Hz, 1H), 4.45 (s, 1H), 5.21 – 5.23 (m, 1H), 5.69 (d, *J* = 8.1 Hz, 1H), 6.68 (d, *J* = 9.2 Hz, 2H), 6.78 (d, *J* = 9.2 Hz, 2H), 6.81 – 6.85 (m, 1H), 7.16 – 7.18 (m, 2H), 7.38 – 7.42 (m, 3H), 7.45 – 7.49 (m, 2H), 8.55 (d, *J* = 4.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.51, 42.71, 47.84, 49.14, 55.56, 59.73, 64.05, 114.97 (3C), 123.92 (2C), 126.77 (2C), 128.84, 129.13 (2C), 131.36 (2C), 132.88, 140.07 (2C), 149.25 (2C), 149.69, 152.70, 175.70, 176.16; IR (KBr)/cm^{-1} 3425, 2924, 2847, 1796, 1597, 1504, 1458, 1381, 1250, 1188, 1041; HRMS (ESI): Calcd for $C_{28}H_{25}N_3O_4$ (MH^+) 468.1923; Found: 468.1925. $[\alpha]_D^{25}$ = – 32 (*c* 0.1, CH_2Cl_2).

(3a*S*,4*S*,7*S*,7a*R*)-7-(hydroxymethyl)-9-(4-methoxyphenyl)-2-phenyl-8-(thiophen-2-yl)-3a,4,7,7a-tetrahydro-1*H*-4,7-(epiminomethano)isoindole-1,3(2*H*)-dione: (45q)



Brown solid, (66% yield), MP = 224 – 227 ^{o}C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.42 (t, *J* = 5.9 Hz, *J* = 6.0 Hz, 1H), 3.38 (d, *J* = 8.2 Hz, 1H), 3.69 – 3.73 (m, 4H), 3.85 (dd, *J* = 11.9, *J* = 5.7 Hz, 1H), 4.23 (dd, *J* = 12.0, *J* = 4.9 Hz, 1H), 4.71 (s, 1H), 5.10 – 5.12 (m, 1H), 5.87 (d, *J* = 8.1 Hz, 1H), 6.79 – 6.82 (m, 3H), 6.84 – 6.88 (m, 2H), 6.99 (t, *J* = 4.1 Hz, 4.4

Hz, 2H), 7.17 – 7.19 (m, 4H), 7.38 – 7.42 (m, 1H), 7.45 – 7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.54, 42.51, 48.06, 49.32, 55.60, 60.83, 62.26, 114.92 (2C), 115.31 (2C), 1265.31, 125.93, 126.33 (2C), 126.46, 128.86, 129.18 (2C), 131.43, 132.27, 133.09, 140.47, 145.40, 152.84, 175.89, 176.68; IR (KBr)/cm^{-1} 3433, 3078, 2924, 2854, 1697, 1605, 1504, 1381, 1196, 1034, 710; HRMS (ESI): Calcd for $C_{27}H_{24}N_2O_4S$ (MH^+) 473.1535; Found: 473.1534. $[\alpha]_D^{25}$ = – 14 (*c* 0.1, CH_2Cl_2).

5.8 Crystal structure of (45b):

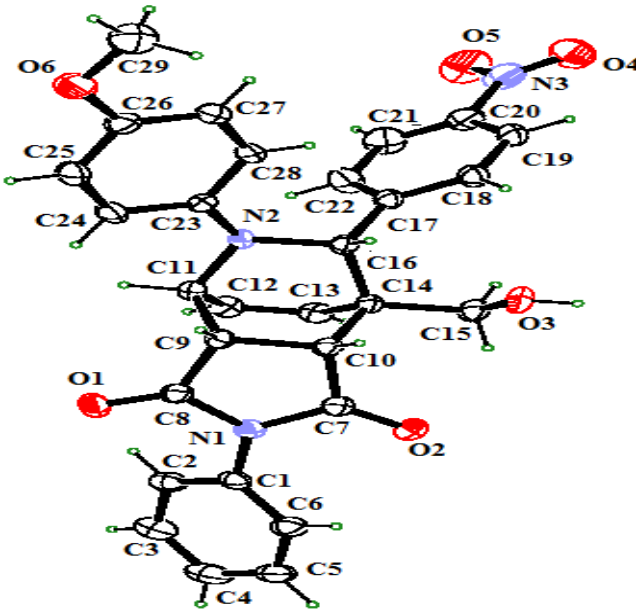
The structure of the compound was established by X-ray diffraction studies. The compound crystallizes in the Monoclinic space group $P2_1$ with unit cell parameters: a =13.0203(14), b =6.0434(6), c = 16.2047(18) Å, β =101.800(11)º and Z= 2. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data and refined to R = 0.0431 for 2751 observed reflections. The crystal packing is dominated by O-H…O and C-H…O hydrogen bonds which link the molecules into infinite chains.

Crystal Structure Determination and Refinement

X-ray intensity data of 4925 reflections (of which 3541 unique) were collected at 293(2) K *X'calibur system – Oxford diffraction make, U.K.* equipped with graphite monochromated Mo*Kα* radiation (λ=0.71073 Å). The crystal used for data collection was of dimensions 0.3 x 0.2 x 0.1 mm. The cell dimensions were determined by least-squares fit of angular settings of 1399 reflections in the θ range 3.84 to 27.65 ^{o}**.** The intensities were measured by ω scan mode for θ ranges 3.61 to 26.00 ^{o}. 2751 reflections were treated as observed (I > 2σ(I)). Data were corrected for absorption, Extinction and Lorentz and polarisation factors. The structure was solved by direct methods using SHELXS97 [1]. All non-hydrogen atoms of the molecule were located in the best E-map. Full-matrix least-squares refinement was carried out using SHELXL97 [1]. All the hydrogen atoms were geometrically fixed and allowed to ride on their parent carbon atoms with C-H= 0.93-0.98 Å with $U_{iso}(H) = 1.2U_{eq}(C)$. The final refinement cycles converged to an R = 0.0437 and wR (F^2) = 0.0888 for the observed data. Residual electron densities ranged from - 0.227 to 0.181 e$Å^{-3}$. Atomic scattering factors were taken from International Tables for X-ray Crystallography (1992, Vol. C, Tables 4.2.6.8 and 6.1.1.4).

Table 5.4 Crystal and experimental data of **45b**

CCDC No	
Crystal description	rectangular
Crystal colour	green
Crystal size	0.30 x 0.20 x 0.10 mm
Empirical formula	$C_{29}\ H_{25}\ N_3\ O_6$
Formula weight	511.52
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a=13.0203(14), b=6.0434(6), c=16.2047(18)Å, β=101.800(11)º
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell volume	1248.2(2)
No. of molecules per unit cell, Z	2
Temperature	293(2)
Absorption coefficient	0.097 mm^{-1}
F(000)	536
Scan mode	ω scan
θ range for entire data collection	3.61<θ<26.00 º
Range of indices	h= -12 to 16, k= -7 to 4, l= -16 to 19
Reflections collected / unique	4925 / 3541
Absorption correction	Multi-scan Crys Alis RED
Reflections observed (I > 2σ (I))	2059
R_{int}	0.0295
R_{sigma}	0.0575
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	340
No. of Restraints	1
Final R	0.0431
wR(F^2)	0.0852
Weight	$1/[\sigma^2(F_o^2)+(0.0353\ P)^2+0.0000P]$ where $P=[F_o^2+2F_c^2]/3$
Goodness-of-fit	1.001
$(\Delta/\sigma)_{max}$	0.001 (tors H29A)
Final residual electron density	$-0.227<\Delta\rho<0.181 eÅ^{-3}$
Measurement	*X'calibur system – Oxford diffraction make, U.K.*
Software for structure solution:	SHELXS97 (Sheldrick, 2008)
Software for refinement:	SHELXL97 (Sheldrick, 2008)
Software for molecular plotting:	ORTEP-3 (Farrugia, 2012) PLATON (Spek, 2009)



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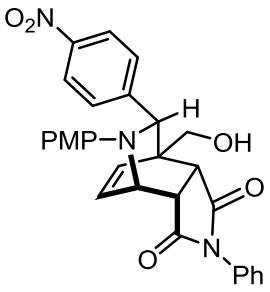


45b

References for crystal data:

1. G. M. Sheldrick, *Acta Cryst.*, **2008**, *A64*, 112.

2. L. J. Farrugia, *J. Appl. Cryst.*, **2012**, *45*, 849-854.

3. A. L. Spek, *Acta Cryst.*, **2009**, *D65*, 148–155.

4. M. Nardelli, *J Appl. Cryst.*, **1995**, *28*, 659.

5. F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, and R. Taylor, *J. Chem. Soc., Perkin Trans-II*, **1987**, S1.

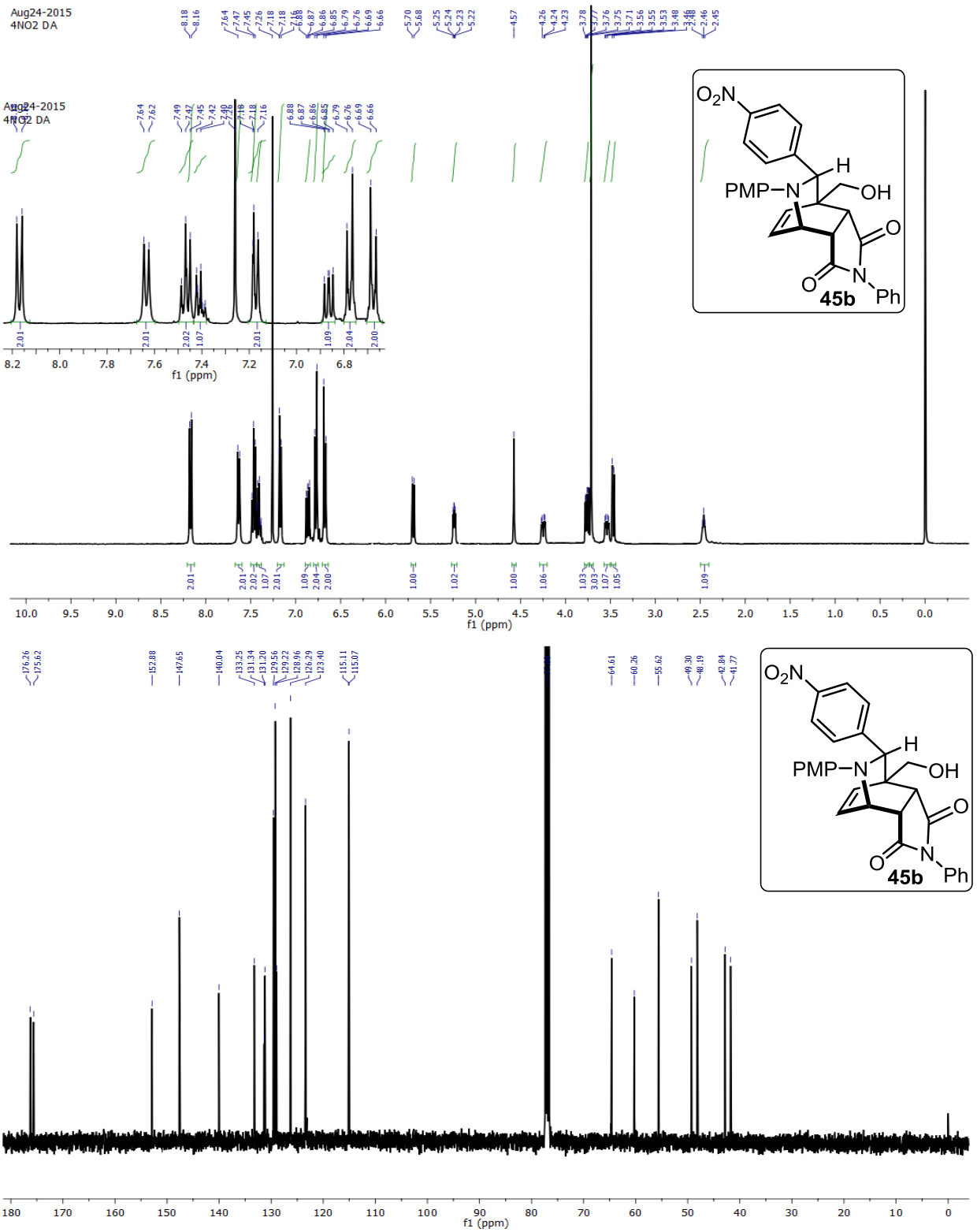
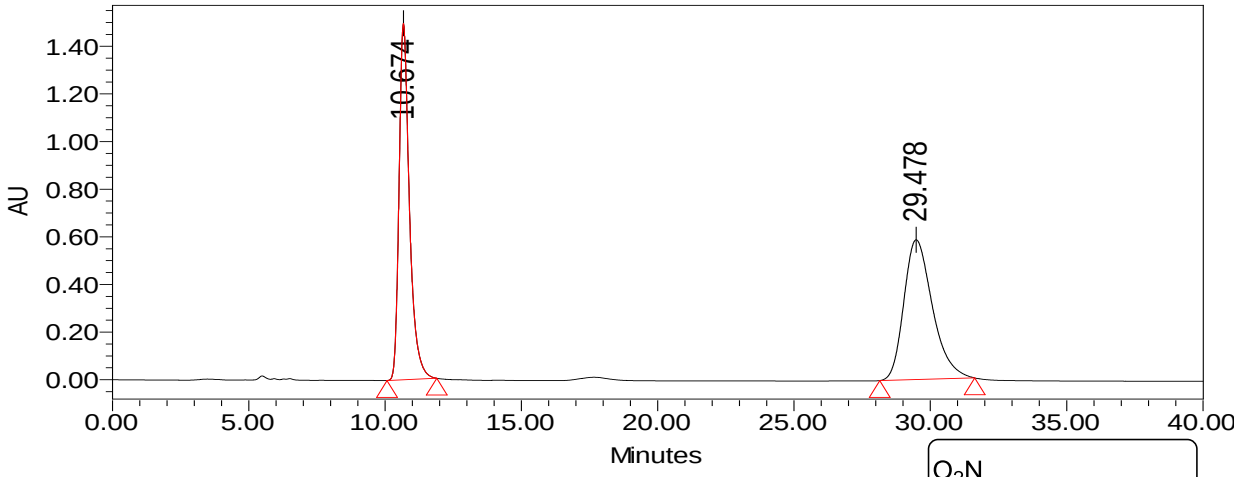
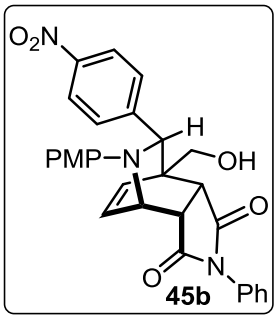
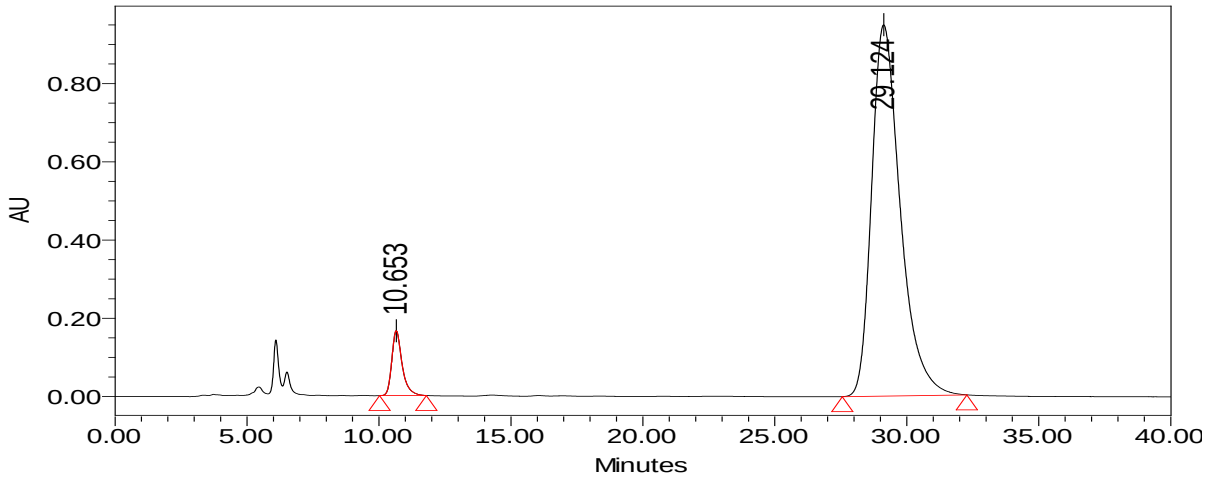


Figure 5.5 ^{1}H and ^{13}C NMR spectra of **45b**



	Retention Time	Area	% Area	Height
1	10.674	39649193	48.13	1496480
2	29.478	42728989	51.87	586839





	Retention Time	Area	% Area	Height
1	10.653	4504194	5.92	165739
2	29.124	71608758	94.08	948853

Figure 5.6 HPLC chromatogram of **45b**

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Chapter - 6

Conclusions

6.1 General Conclusions

The current thesis entitled "**Organocatalytic Synthesis of Six Membered Nitrogen Heterocycles and Related Alkaloids"** deals with the synthesis of some selected six-membered nitrogen heterocycles and related *N*-fused heterocycles in asymmetric fashion by employing organocatalyzed direct Mannich [4+2] cyclization cascade process in multi-bond forming reactions like multi-component reactions, tandem sequences and also utilizing one-pot operations. The thesis demonstrated the synthesis of 2,3-disubstituted piperdines, 2,3-diisubstituted 1,2-dihydropyridines, 2,3-disubstituted 1,2,5,6-tetrahydropyridines, and aza-bicyclic isoquinuclidines in individual chapters respectively.

The work described in this thesis is the development of enantioselective Mannich reactions of carbonyl compounds using covalent organocatalysis. L-Proline was found to catalyze the reaction with excellent enantiocontrol for a wide variety of piperidines. The analysis of the products using NMR and ORTEP techniques enabled the rationalization of the relative and absolute stereochemistry of products. Preliminary investigations on the annulation using this organocatalytic system demonstrated significant potential of the method for the enantioselective formation of nitrogen heterocycles with several stereocenters along with their relative alkaloids synthesis.

Several efforts are contributed for the organic synthesis to access the potent organic complex structures in a reduced number of synthetic steps from the simple and readily available precursors. In general, the protocols such as tandem or domino sequences, multi-component reactions and one-pot sequential reactions are given high priority in synthetic organic chemistry. The development of one pot methodologies to overcome the multistep syntheses is the main advantage of the present research work. Moreover, in modern synthetic field, organocatalyzed functionalization of compound through C-C, C-N, bond formation is of great interest. Organocatalysis is turned into a most powerful tool for the construction of heterocyclic moieties and small molecule natural products (SMNPs). Since the organocatalysis is considered as a greener catalysis when compared with other metal and acid catalysis, main efforts are devoted to develop bench stable, open vessel reaction conditions even using water as solvent for environmental requirements. Most of the organocatalytic methods described in the previous chapters offer the C-C and C-heteroatom bond formations with high efficiencies, high functional

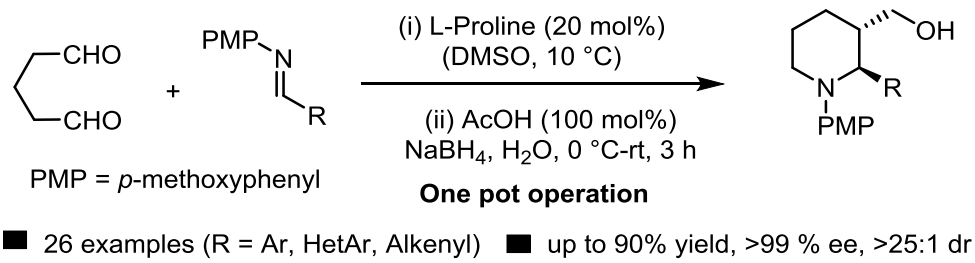
group tolerance and excellent stereo-, chemo- and regioselectivities. Consequently, synthesis of potent heterocyclic motifs by employing atom-economical formal cycloaddition reactions through organocatalysis has become the most appreciated task for the sustainable chemical synthetic routes.

6.2 Specific Conclusions

The thesis entitled "**Organocatalytic Synthesis of Six Membered Nitrogen Heterocycles and Related Alkaloids**" is divided into five chapters. A brief overview of these chapters is discussed below.

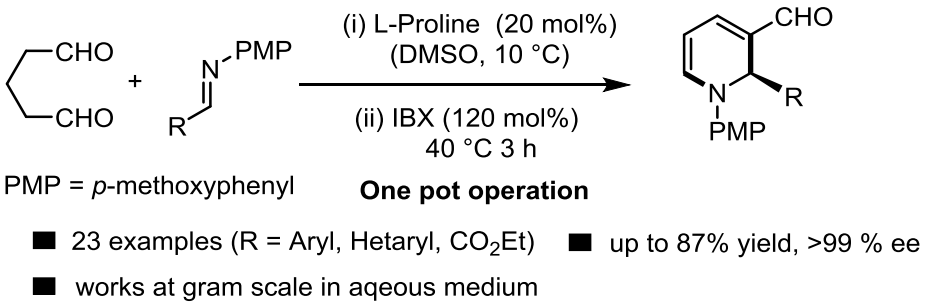
First chapter: This chapter covered the origin of organocatalysis and its contribution as a green process in the synthetic chemistry from the past decade along with its significant role in the development of diverse synthetic methods complex scaffolds, synthetic drugs and natural products. Classification of organocatalysis and the role of covalent, non-covalent modes of activations of the substrates is described. The development and progress on amine catalyzed direct Mannich reaction and its application to prepare nitrogen containing compounds were discussed. In additions, this chapter also covers the importance of glutaraldehyde as an important bifunctionalized dicarbonyl compound for amine catalyzed domino/cascade reactions to prepare biologically important complex scaffolds.

Second chapter: This chapter revealed a rational design and synthesis of novel enantioselective piperidines. Synthetic methods to prepare piperidines involving imine as suitable substrate for [4+2] cycloaddition/annulation reaction with various 1,4-carbon dipoles were discussed. Our contribution in this direction as [4+2] annulation between imines and glutaraldehyde was discussed thoroughly, where glutaraldehyde acts as 1,4-carbon donor-acceptor (D-A) precursor under amine catalysis. This one pot approach involves proline catalyzed direct *syn*-Mannich reaction and $NaBH_4$ mediated *in situ* reductive cyclization between glutaraldehyde and imines produced substituted piperidine in high yields and excellent stereoselectivity. The reactions provide substituted chiral piperidines from readily available material under mild conditions. The practical utility of the developed method was further shown at gram scale reaction, as well as quick synthesis of functionalized (-)-anabasine, which is a nicotine based alkaloid having the anti-insecticide potency.



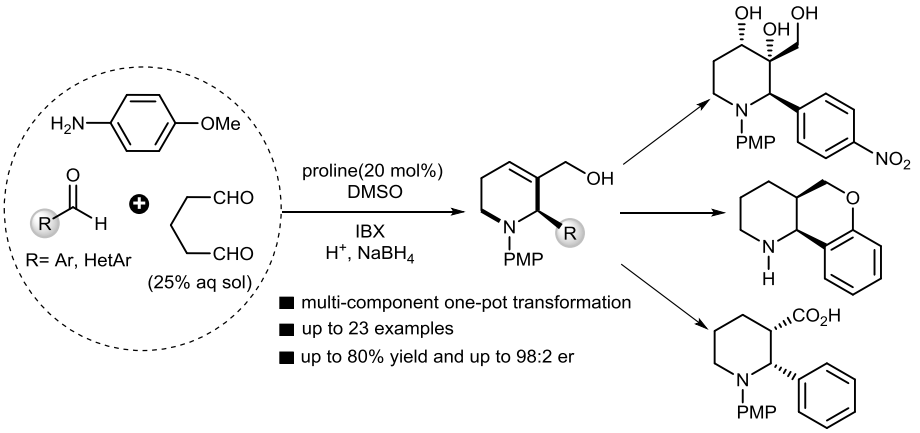
Scheme 6.1 Proline Catalyzed enantioselective synthesis of functionalized piperidines

Third chapter: This chapter disclosed a [4+2] annulation reaction for the enantioselective synthesis of 1,2-dihydropyridines (DHPs), which are very useful precursors for the synthesis of several chiral complex quinolizidines, isoquinuclidines. This one pot method also involves an amine catalyzed direct Mannich reaction/cyclization sequence between glutaraldehyde and imines, followed by IBX mediated site selective oxidation of in situ generated enamine compound to afford 1,2-DHPs in high yields and selectivity. The use of the developed method was successfully demonstrated by the synthesis of a challenging enantioselective octahydro[1,6] napthyridines. Moreover, the synthesis of both the enantiomers of chiral 1,2-dihydropyridines (DHPs) was also achieved at gram scale.



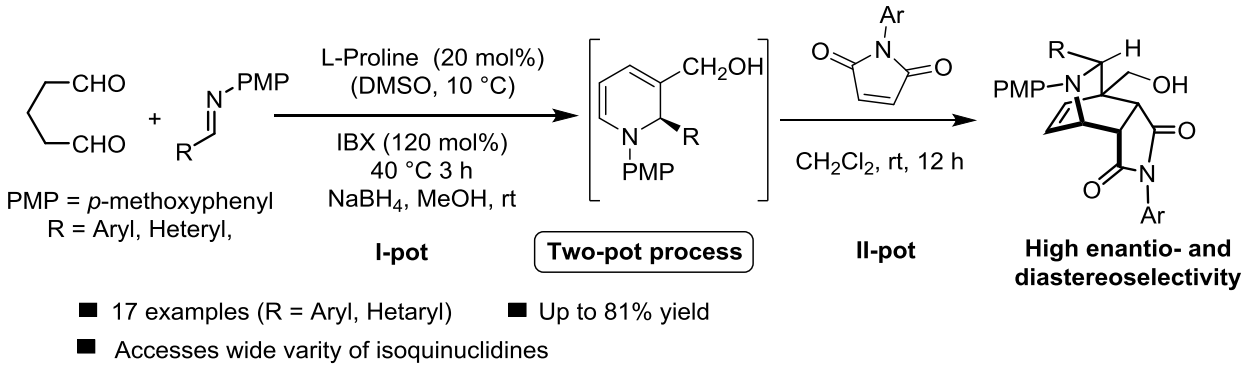
Scheme 6.2 Proline catalyzed enantioselective synthesis of 1,2-dihydropyridines

Fourth chapter: This chapter demonstrated an amine catalyzed enantioselective synthesis of 1,2,5,6-tetrahydropyridines (THPs) from glutaraldehyde and imines through [4+2] annulation/oxidation/reduction sequence in one pot operation. These compounds are very useful precursors for the synthesis of several chiral complex molecules such as imino sugars and related alkaloids. Therefore, we have also shown the application of this method for the asymmetric synthesis of medicinally important compounds like; synthesis of nipecotic acid derivatives, guacine analogues and pipicolic acid isomers along with the regio-isomer of 2-Epi-CP-99 994.



Scheme 6.3 Proline catalyzed multicomponent synth/esis of chiral 1,2,5,6-tetrahydropyridines

Fifth chapter: This chapter disclosed an efficient approach for the quick synthesis of isoquinuclidines *via* enantio- and diastereoselective Diels-Alder reaction between dienamine and various dienophiles. This method involved as amine catalyzed [4+2] annulation between imines and glutaraldehyde and oxidation/reduction sequence to yield dienamine alcohol, which was used further without isolation for Diels-Alder reaction with *N*-phenylmalimide to afford isoquinuclidines in two-pot operations with good yield and high selectivity. These isoquinuclidines are useful synthetic scaffolds for synthesizing oseltamivir drug analogues and other complex natural products such as *iboga*-alkaloids.



Scheme 6.4 Proline catalyzed enantio- and diastereoselective two-pot synthesis of isoquinuclidines

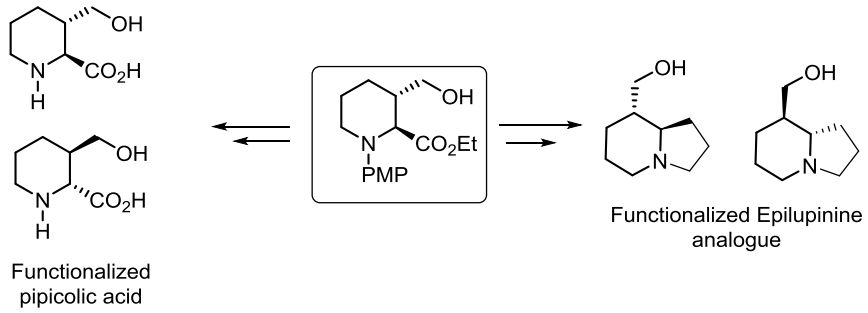
6.3 Future Scope of the Research Work

Organocatalyzed transformations deliver C-C and C-N bond formation without the necessity of pre-functionalization of substrates is undoubtedly a valuable tool for the construction of diverse molecular frameworks and related hybrid scaffolds which have a wide range of applications in chemistry and biology. In addition, organocatalytic multi-bond forming approaches like tandem

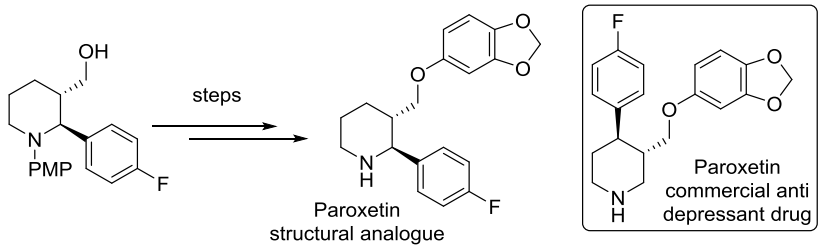
reactions, multi-component reactions and one-pot domino sequences for the synthesis of highly complex molecules is highly appreciable. Fused heterocyclic ring systems are present as core system for several important natural products and pharmacologically active drugs. Therefore, the synthesis of these molecules by using organocatalytic approaches can be a potential alternative to traditional multi-steps synthesis.

The thesis is mainly focused on the development of new catalytic methods for the synthesis of nitrogen heterocycles such as substituted piperdines, 1,2-dihydropyridines (DHPs), tetrahydropyridines (THPs), and aza-bicyclic isoquinuclidines in individual chapters. Further, exploration of these methodologies to synthesize polycyclic compounds, which are having tremendous applications in medicinal chemistry as well as in biological sciences, is possible. The developed organocatalytic direct Mannich/cyclization sequence as [4+2] annulation for the synthesis of the key nitrogen heterocycles may have application in the synthesis of wide range of medicinally important compounds.

The method described in Chapter-2 for piperidines synthesis may be used for the synthesis of chiral pipicolic acid derivatives. The methodology can also be utilized for the synthesis of chiral quinolizidines. Further efforts to prepare important *N*-heterocyclic compounds using our developed methods are going-on. The immediate efforts in this direction are shown in **Scheme 6.5 and 6.6.**



Scheme 6.5 Future scope for the synthesis of pipicolic acids and epilupinine analogues



Scheme 6.6 Future scope for the synthesis of Paroxetin analogue

List of publications [A-1]

1. Nisar A. Mir, Sachin Choudhary, **P. Ramaraju**, Deepika Singh and Indresh Kumar. Microwave assisted aminocatalyzed [3+2] annulation between α-iminonitriles and succinaldehyde: Synthesis of pyrrole-3-methanols and related polycyclic ring systems. ***RSC Adv.* 2016, *6,* 39741-39749.**
2. **P Ramaraju**, NA Mir, D Singh, VK Gupta, R Kant, I Kumar, Enantioselective Synthesis of N-PMP-1, 2-dihydropyridines via Formal [4+ 2] Cycloaddition between Aqueous Glutaraldehyde and Imines, ***Org. let.* 2015, 17, 5582-5585.**
3. Indresh Kumar**, P. Ramaraju,** Nisar A. Mir and Anoop Singh; Linear dialdehydes as promising substrates for aminocatalyzed transformations; ***Org. Biomol. Chem.***, **2015, 13, 1280-1293**.
4. Indresh Kumar**,** N. A. Mir, **P. Ramaraju**, D. Singh, V. K. Gupta and Rajnikant; Direct catalytic synthesis of densely substituted 3-formylpyrroles from imines and 1,4-ketoaldehydes; ***RSC Adv***. **2014, 4, 34548-34551.**
5. Indresh Kumar, **P. Ramaraju,** Nisar A. Mir, V.K. Gupta, and Rajnikant. Highly Enantioselective [4+2] Annulation *via* Organocatalytic Mannich-reductive Cyclization: One-pot Synthesis of Functionalized Piperidines; ***Chem. Commun.*2013, 49, 5645-5647.**
6. Indresh Kumar**, P. Ramaraju,** Nisar. A. Mir. Asymmetric Trienamine Catalysis: New Opportunities in Amine Catalysis. ***Org. Biomol. Chem. 2013,* 11, 709-716.**
7. Indresh Kumar, Nisar A. Mir**, P. Ramaraju,** Basant P. Wakhloo. Organocatalytic Mannich/cyclization/ aromatization sequence: direct synthesis of substituted pyrrole-3-carboxaldehydes. ***RSC Advances***. **2012, 2, 8922-8925**.

List of presentations [A-2]

1. **P. Ramaraju,** Nisar A. Mir, Indresh Kumar. "Highly Enantioselective [4+2] Annulation *via* Organocatalytic Mannich-reductive Cyclization: One-pot Synthesis of Functionalized Piperidines" at ISRAM-2014, NIPER, Mohali, Punjab, India, September 8 – 10, 2014.(Poster presentation)
2. **P. Ramaraju,** Nisar A. Mir, Indresh Kumar. "Highly Enantioselective [4+2] Annulation *via* Organocatalytic Mannich-reductive Cyclization: One-pot Synthesis of Functionalized Piperidines" at NFM-2014, Bits Pilani, Pilani campus, Rajasthan, India, November 7 – 8, 2014. (Oral presentation)
3. **P. Ramaraju,** N. A Mir, I Kumar, "Enantioselective Synthesis of N-PMP-1, 2-dihydropyridines via Formal [4+ 2] Cycloaddition between Aqueous Glutaraldehyde and Imines" at NDCS-2015, Bits Pilani, Pilani campus, Rajasthan, India, October 16 – 18, 2015.(Poster presentation)
4. **P. Ramaraju,** N. A Mir, I Kumar, "Enantioselective Synthesis of N-PMP-1, 2-dihydropyridines via Formal [4+ 2] Cycloaddition between Aqueous Glutaraldehyde and Imines" at ISCBC-2016, Uka Tarsadia University, Surat, Gujarat, India, February 6 – 8, 2016.(Poster presentation)

Brief biography of the candidate [A-3]

Panduga Ramaraju was born in Mahabubnagar, Telangana, India. He completed his Master's degree (organic chemistry) from Osmania University, Hyderabad during 2009. In june 2011, he was awarded UGC-JRF in chemical sciences by UGC-New Delhi, Govt. of India. In March 2012, he joined the Department of Chemistry, BITS Pilani for Ph.D under the guidance of **Dr. Indresh Kumar**. In March 2014, he was awarded UGC-SRF in chemical sciences by UGC-New Delhi, Govt. of India. He has published six research articles in peer reviewed international journals and some more are communicated and few others are under manuscript preparation. He presented his papers in many national/international conferences/symposiums. His research interest lies in the **"Development of new methods for the synthesis of asymmetric as well as non-asymmetric bioactive nitrogen heterocycles and related alkaloids along with the fused heterocyclic natural products through organocatalysis"**.

Brief biography of the supervisor [A-4]

Dr. Indresh Kumar is Assistant Professor of Chemistry at the Birla Institute of Technology and Science, Pilani. Dr. Indresh Kumar did his B.Sc. (Chemistry) and M.Sc. (Organic Chemistry) from Ch. Charan Singh University, Meerut (U.P) India. He completed his PhD degree in Organic Chemistry from National Chemical Laboratory (CSIR), Pune with Dr. C. V. Rode (Scientist-F) during 2007-08. He did his Post-doctoral research work with Prof. Yujiro Hayashi at Tokyo University of Sciences, Tokyo. He joined at Shri Mata Vaishno Devi University, Katra, (J&K), India as Assistant Professor in Chemistry from 2009 and continued till January 2012.

Dr. Indresh Kumar is recipient of Award of "IASc-INSA-NASI Summer Research Fellowship in 2011, Award of "INSA-Visiting Scientist Fellowship-2013" by INSA-New Delhi, Award of "Outstanding Potential for Excellence in Research and Academics (OPERA)" during 2014-15 from BITS Pilani, ISCB Young Scientist award in Chemical Sciences from Indian Society of Chemists and Biologists, Lucknow for 2016. He has 12 years of research experience and 8 years of teaching experience. Dr. Kumar has authored 27 research paper in the peer-reviewed international journals in the area of synthetic organic chemistry. His research work has been widely recognized and highly cited in the scientific community. He has participated in several national and international symposia/conferences and delivered more than 30 invited lectures. He is currently supervising four Ph.D students. He has completed three research projects as Principle Investigator sponsored by UGC, DST New Delhi and BITS Pilani. Currently, he has one major project from BITS Pilani He has also served as a reviewer for several journals. He is life the member of Indian Society of Chemists and Biologists, Lucknow and Chemical Research Society of India, Bangalore.

His main research interests are asymmetric organocatalysis, development of new synthetic methodology, and total synthesis of biologically active compounds.

PUBLICATIONS

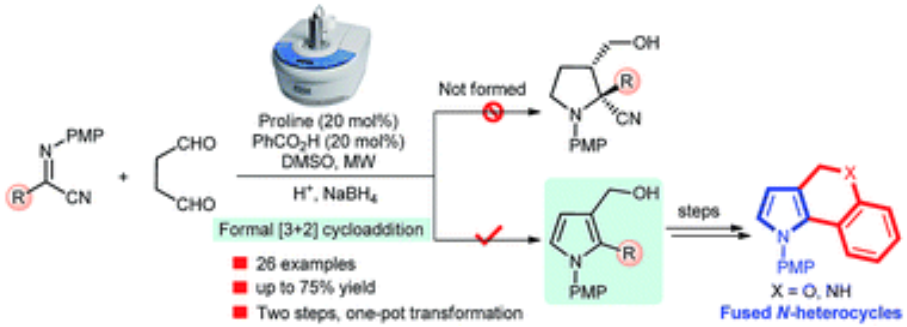
RSC Advances

PAPER

Cite this: *RSC Adv.*, 2016, **6**, 39741

Microwave assisted aminocatalyzed [3 + 2] annulation between α-iminonitriles and succinaldehyde: synthesis of pyrrole-3-methanols and related polycyclic ring systems†

Nisar A. Mir,[a] Sachin Choudhary,[a] Panduga Ramaraju,[a] Deepika Singh[b] and Indresh Kumar*[a]



Organic LETTERS

Letter

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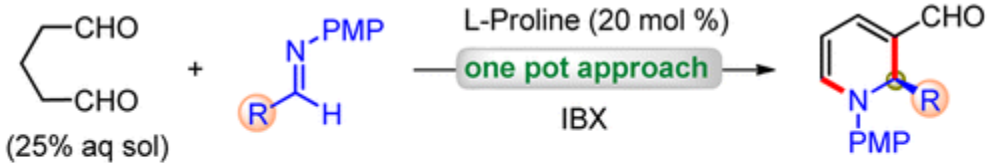
Enantioselective Synthesis of *N*-PMP-1,2-dihydropyridines via Formal [4 + 2] Cycloaddition between Aqueous Glutaraldehyde and Imines

Panduga Ramaraju,[†] Nisar A. Mir,[†] Deepika Singh,[‡] Vivek K. Gupta,[§] Rajni Kant,[§] and Indresh Kumar*[,†]

[†]Department of Chemistry, Birla Institute of Technology and Science, Pilani 333 031, Rajasthan India

[‡]Instrumentation Division, IIIM-CSIR Laboratory, Jammu 180 001, Jammu and Kashmir, India

[§]X-ray Crystallography Laboratory, Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu 180 006, Jammu and Kashmir, India



- Metal free one pot process
- Mild reaction conditions in presence of H_2O
- R = Aryl, HetAryl, CO_2Et
- Highly efficient even at gram scale

23 examples
up to 87% yields
up to >99:1 er

PUBLICATIONS

Organic & Biomolecular Chemistry

REVIEW

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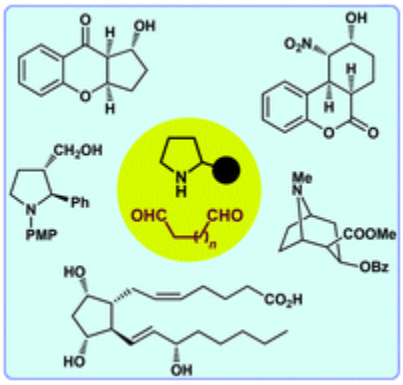
Linear dialdehydes as promising substrates for aminocatalyzed transformations

Cite this: *Org. Biomol. Chem.*, 2015, **13**, 1280

Indresh Kumar,* Panduga Ramaraju, Nisar A. Mir and Anoop Singh



RSC Advances

COMMUNICATION

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Direct catalytic synthesis of densely substituted 3-formylpyrroles from imines and 1,4-ketoaldehydes†‡

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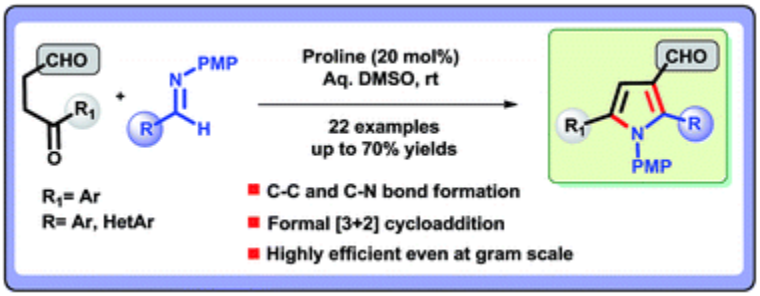
Indresh Kumar,*[a] Nisar A. Mir,[a] Panduga Ramaraju,[a] Deepika Singh,[b] Vivek K. Gupta[c] and Rajnikant[c]



PUBLICATIONS

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Highly enantioselective [4+2] annulation *via* organocatalytic Mannich-reductive cyclization: one-pot synthesis of functionalized piperidines†

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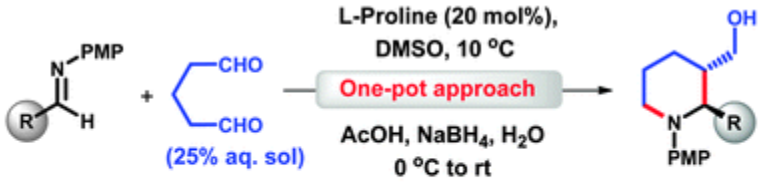
Indresh Kumar,*[a] Panduga Ramaraju,[a] Nisar A. Mir,[a] Deepika Singh,[b] Vivek K. Gupta[c] and Rajnikant[c]



- 26 examples (R = Aryl, hetaryl, Alkenyl)
- up to 90% Yields, up to >25:1 de, ee >99%
- Work efficiently at gram scale

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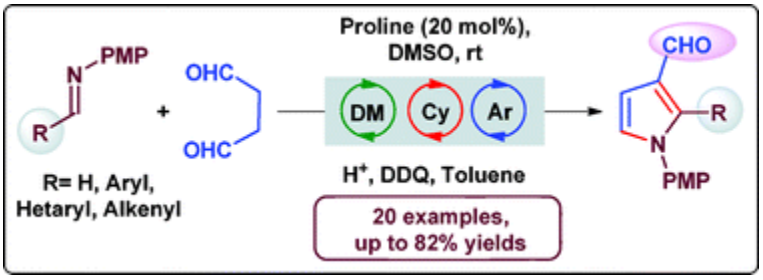
COMMUNICATION

Organocatalytic Mannich/cyclization/aromatization sequence: direct synthesis of substituted pyrrole-3-carboxaldehydes†‡

Indresh Kumar,*[ab] Nisar A. Mir,[a] Panduga Ramaraju[a] and Basant P. Wakhloo[c]



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