Organocatalytic Approach Towards the Synthesis of Five Membered Nitrogen Heterocyclic Compounds

THESIS

Submitted in partial fulfillment of the requirements for the degree

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DOCTOR OF PHILOSOPHY

by

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Under the supervision of

Dr. Indresh Kumar

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE

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Dedicated to

My Highly Respected

Brother

Mr. Javid Ahmad Mir

And My Mother

Begum Zoona

BIRLA INSTITUTE OF TECHNOLOGY AND SCIENCE
PILANI (RAJASTHAN)

CERTIFICATE

This is to certify that the thesis entitled "**Organocatalytic Approach Towards the Synthesis of Five Membered Nitrogen Heterocyclic Compounds**" submitted by Mr. Nisar Ahmad Mir ID No 2012PHXF020P for the award of Ph.D. Degree of the Institute embodies the original work done by him under my supervision.

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Signature in full of the Supervisor:
Name: **Dr. INDRESH KUMAR**
Designation: Assistant Professor

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Thank you all,

Nisar Ahmad Mir

ABSTRACT

Nitrogen-containing heterocyclic compounds have been known to have a tremendous potential in multidisciplinary fields. The work mentioned in this thesis entitled "**Organocatalytic approach towards the synthesis of five-membered nitrogen heterocyclic compounds**" deals with the synthesis of some selected five-membered nitrogen heterocycles such as substituted pyrrolidines, pyrroles, pyrrolo-pyridazinones in asymmetric as well as in non-asymmetric fashion. The main strategy involves [3+2] annulation between succinaldehyde or 1, 4-ketoaldehydes, with various *N*-PMP-aldimines, which involves amine catalyzed direct Mannich reaction followed by reductive or oxidative cyclization sequence. Here these dicarbonyl compounds succinaldehyde or 1, 4-ketoaldehydes acts as 1, 3-carbon *donor-acceptor* (D-A) precursors for the one-pot domino/tandem sequence with imines. This thesis is divided into six chapters.

The first chapter of the thesis presents a brief discussion on organocatalysis, particularly, amine-catalyzed direct Mannich reactions, its progress in the development of synthetic methods for complex scaffolds, synthetic drugs, and natural products. A brief description on five membered *N*-nitrogen heterocycles and the discussion on the utilization of succinaldehyde in aminocatalytic cascade transformations are also presented.

The second chapter of the thesis describes the asymmetric synthesis of *trans*-2, 3-disubstituted pyrrolidines, and related natural product based scaffolds *via* proline catalyzed [3+2] annulations between succinaldehyde and aldimines. This reaction proceeds through the direct Mannich reaction followed by reductive cyclization under mild conditions with high yield and enantioselectivity. The synthetic application of this developed method is also shown to prepare highly functionalized and fused pyrrolidines which are present in medicinally important compounds.

The third chapter of the thesis describes the synthesis of 2, 3-disubstituted-3-formylpyrroles by proline catalyzed direct Mannich reaction/oxidative cyclization as formal [3+2] cycloaddition process. The chapter is divided into two parts.

In part-A, a two pot strategy is described for the synthesis of 2, 3-disubstituted pyrrole-3-carboxaldehyde *via* proline catalyzed direct Mannich cyclization followed by an oxidative aromatization using DDQ as an oxidant with good yields.

ABSTRACT

In part-B, a simple, convenient and improved one-pot procedure has been developed for the synthesis of 2, 3-disubstituted pyrrole-3-carboxaldehydes in multicomponent fashion from sucinaldehyde, aromatic aldehydes, and *p*-anisidine by using IBX as the mild oxidant. The developed high yielding method has been utilized for the quick synthesis of some hybrid-heterocyclic compounds such as pyrrolo-quinolines, pyrrolo-phenanthridines, pyrrolo-oxadiazoles and pyrrolo-acrylates.

The fourth chapter of the thesis describes a highly efficient method for the one-pot synthesis of densely and fully substituted 3-formylpyrroles and related fused heterocycles under proline catalyzed conditions. Herein, direct Mannich reaction between 1, 4-ketoaldehyde and *N*-PMP imines followed by *in situ* cyclization and aerobic aromatization takes place in same pot, thus highly substituted 3-formylpyrroles obtained in good yields. The developed methodology was further applied to construct various fused heterocycles which are having tremendous applications in the field of biology and medicinal chemistry.

The fifth chapter of thesis deals with the synthesis of fused pyrrolo-[2, 3-*d*]pyridazinone derivatives by employing fully organocatalytic two-pot multicomponent cascade approach using ethyl glyoxalate, *p*-anisidine, succinaldehyde and substituted hydrazines as starting material *via* direct Mannich reaction/oxidative aromatization followed by nucleophilic addition/cyclization with various hydrazines in good yields in one-pot. Further applications of this developed methodology lead to the formation of azido-pyrrolo-[2, 3-*d*] pyridazines, which are having significant applications in medicinal chemistry.

Finally, overall thesis work is summarized in chapter six. The future scope of the research work has also been 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
^{1}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 I

Introduction to amine catalysis, direct Mannich reaction, nitrogen heterocycles and succinaldehyde

1.1. Organocatalysis

The term “organocatalyst” is a concatenation of the words “organic” and “catalyst.” The definition corresponds to the acceleration of chemical reactions through the addition of a sub-stoichiometric quantity of an organic compound. 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 in the scientific community in 2000 by MacMillan, in order to describe the field of organic synthesis that utilized low molecular weight simple organic molecule to catalyze given transformations.[3-4]

The organocatalyst could be achiral or chiral and are composed of C, H, N, S, and P. During the last decades, organocatalysis has been included among the most important and a successful concept in 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. 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 one can easily develop organic catalysts. These compounds include α-amino acids, α-hydroxy acids, nucleic acids, and carbohydrates. The uses of small organic molecules as catalysts has experienced an impressive growth recently because of the advantages such as easy availability, easy of carrying out the asymmetric transformation in a metal free environment and under mild reaction condition, are associated with this catalysis.

In fact, the renewal of proline-catalyzed transformations in early 2000 by Barbas III, List and MacMillan[3,11] was the starting 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 and further cycloaddition, substitution, elimination and rearrangement reactions. These types of synthetic processes have contributed significantly 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 part is on organocatalytic direct Mannich reactions.

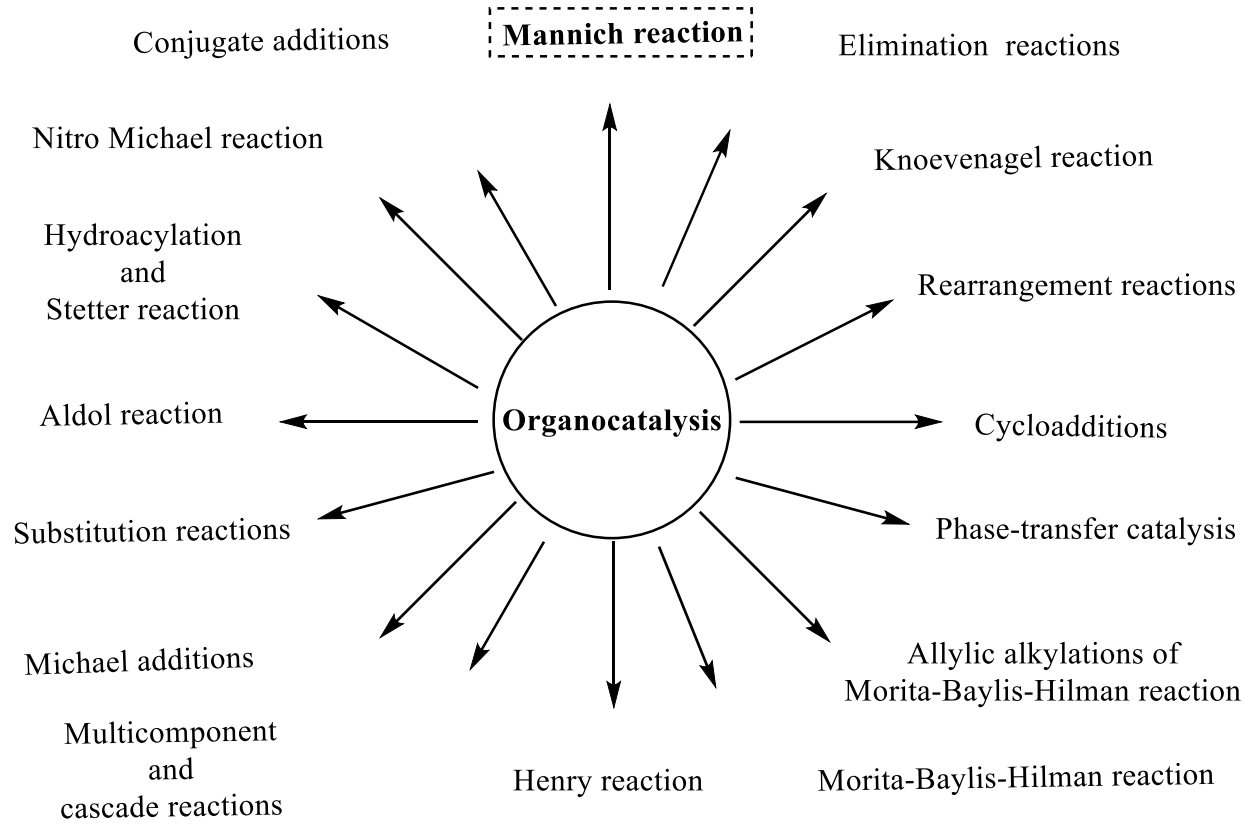


Figure 1.1 Various types of reactions involving organocatalysis

In general, organocatalysts are air and moisture stable and, thus, inert equipment such as vacuum lines or glove boxes are not necessary thus making them more practical for use in synthetic laboratory. These compounds are also readily available, easy to handle, less toxic compared to transition metal, which results the reactions are conducted under mild conditions and minimum waste of organic solvents.[13-14] During the last decade, organocatalysis has been one of the most rapidly growing and competitive fields in asymmetric catalysis and developed to a third pillar beside metal and biocatalysis.[15] In addition to these characteristics, organocatalysts are tolerant of numerous functional groups, seeks to reduce energy consumption, and avoid time-consuming and protecting group manipulations for carrying out such type of chemical transformations.

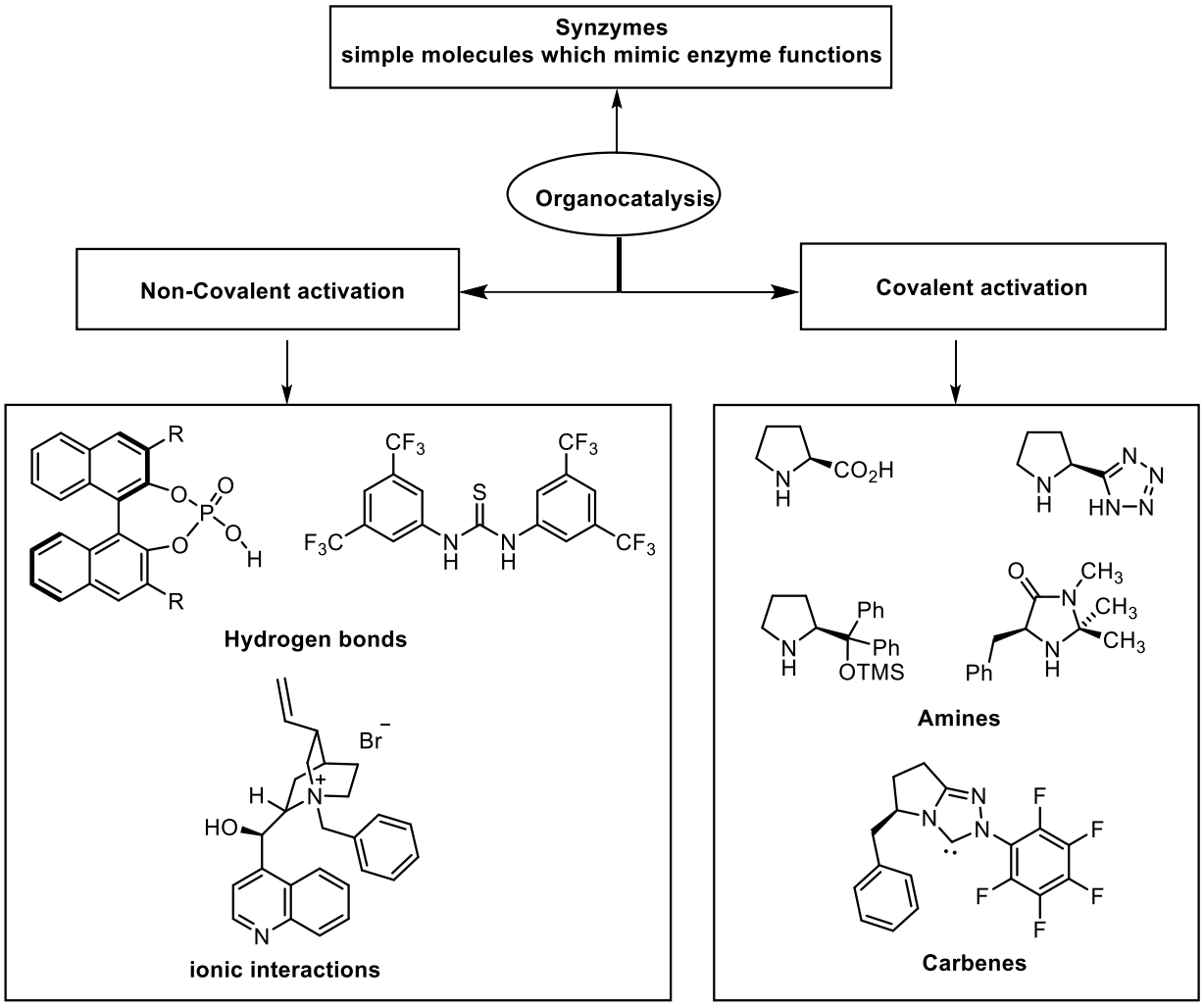


Figure 1.2 General classifications of the organocatalysis

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 achiral 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, a covalent bond between the organocatalyst and the substrate is formed, that increases the interaction between the substrate and the reagent in the reaction. In this category, amine catalysis[16] and carbenes[17] activations 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 already 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 real explosion of aminocatalysis in asymmetric transformations, however, occurred in recent years followed by the widespread recognition of the generality of the concept.

Aminocatalysis today deserves its own classification system. The original enamine and iminium-ion mechanistic paradigms[33] have now been expanded to new activation modes, which include extended enamine catalysis (dienamine[34-36] and trienamine[37-38]) and SOMO (singly occupied molecular orbital) catalysis characterized by the formation of enamine radical cations.[39-42] Here the discussions is restricted to amine catalysis involving enamine and iminium-ion activations as shown in (**Figure 1.3**).

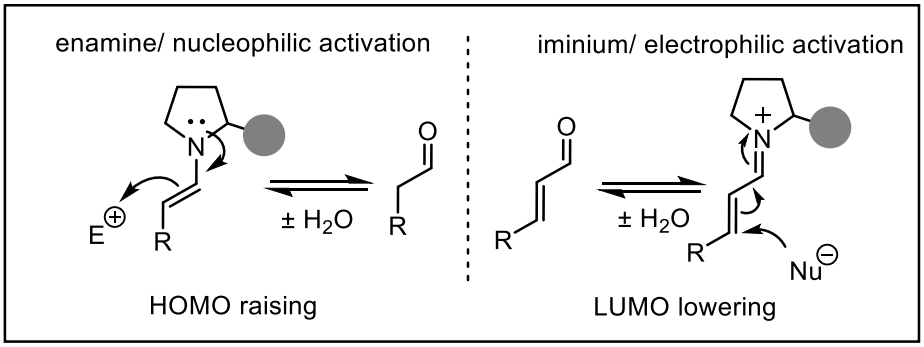


Figure 1.3 Iminium ion and enamine activation modes of amino-catalysis

Among various modes of activation applicable for organocatalysis, amine catalysis proceeds through enamine (HOMO)[39,43-46] and iminium-ion (LUMO)[3] activations have emerged as a major contributor to the exponential growth of this area as shown in (**Figure 1.4**). Following the turn of the millennium, the role of asymmetric covalent aminocatalysis has developed into a scalable, synthetic paradigm stimulate the synthetic community toward utilization of these methods for more practical, metal-free synthesis of natural products.

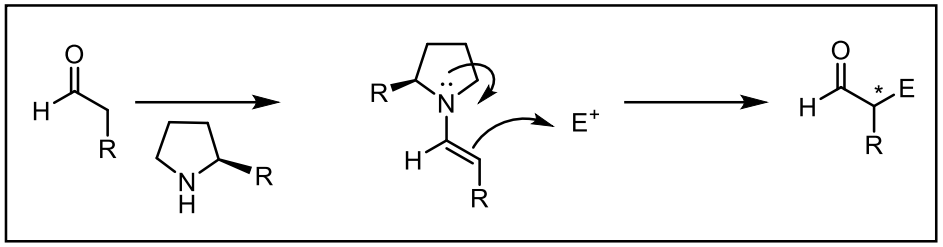
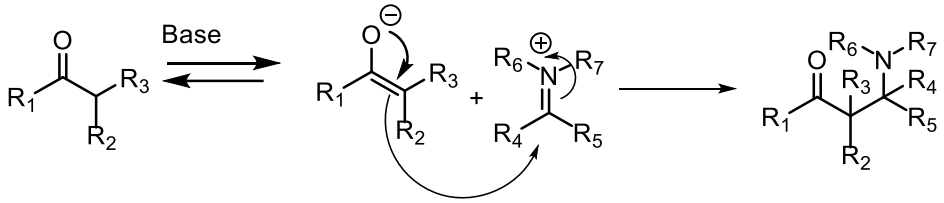


Figure 1.4 Covalent mode of activation of carbonyls through amine catalysis

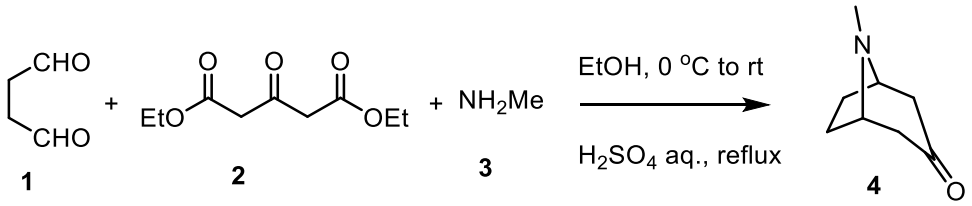
1.3 Mannich Reaction

In practice, Mannich reaction is an organic reaction used to convert a primary or secondary amine and two carbonyl compound which involves (one non-enolizable aldehyde and another one are enolizable carbonyl compound as most important nucleophiles,) to *β*-amino carbonyl compound, also known as a Mannich base. This reaction is also called amino alkylation.Mannich reaction is named after a German Chemist *Carl Ulrich Franz Mannich* in 1912. A generalized mechanism is shown below (**Scheme 1.1**).[47]



Scheme 1.1 Simplified Mannich reaction mechanism

The reaction is particularly interesting because of the incorporation of the nitrogen atom in the products, which is often present in medicinally important compounds. In fact, the Mannich reaction was already used in 1917, only five years after its discovery, as a key step in *Robinson*'s total synthesis of tropinone (**4**).[48] In this reaction succinaldehyde (**1**), diethyl acetonedicarboxylate (**2**), and methylamine (**3**) gave the desired product after two fold decarboxylation in a synthesis that is nowadays recognized as a classic in total synthesis (**Scheme 1.2**).

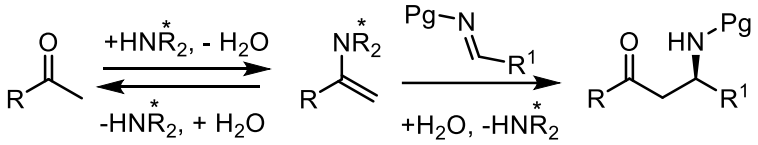


Scheme 1.2 Total synthesis of tropinone by *Robinson*

1.4 Development of amino-catalytic asymmetric Mannich reactions

The asymmetric Mannich reaction is one of the most powerful carbon-carbon bond forming protocol for the construction of nitrogen-containing compounds.[49-55] The utilization of this reaction allows for the preparation of optically enriched *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.[56-59] Traditionally, asymmetric Mannich reactions are catalyzed by chiral transitionmetal complexes.[60-65] But in 2000, List described the first L-proline catalyzed Mannich reaction.[66-67] This landmark discovery stimulated the rapid development of many asymmetric organocatalytic Mannich reactions. The typical organocatalytic approach to asymmetric Mannich reaction is based on enamine activation of carbonyl compounds using secondary amine organocatalysts.[27] Since its discovery, the Mannich reaction was developed into one of the most versatile C-C and C-N bond forming reactions and allows access to a variety of different building blocks and alkaloids.[68-71] In this chapter, the progress on direct asymmetric Mannich reactions involving chiral aminocatalysis is discussed.

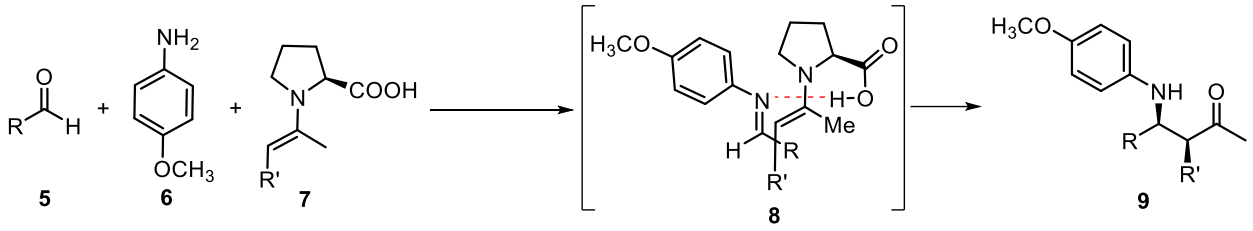
Carbonyl groups can often be efficiently activated towards electrophiles by the addition of primary or secondary amines. The *in situ* formation of the corresponding enamines leads to a more nucleophilic species. Moreover, if the amine is chiral, asymmetric induction can be transferred to the product as shown in (**Scheme 1.3**).



Scheme 1.3 Direct asymmetric Mannich reaction based on enamine catalysis

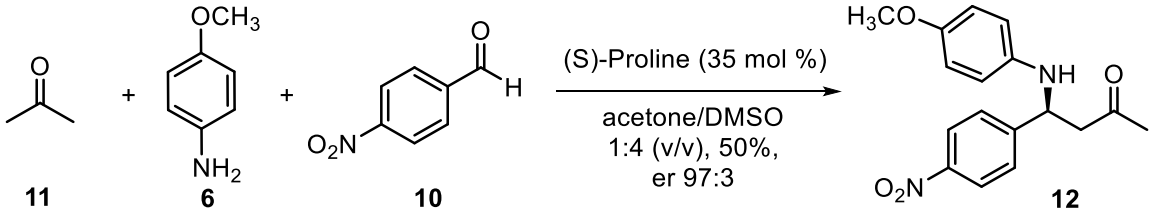
Organocatalytic Mannich reactions can be carried out either as three-component, or as reactions of preformed imines with aldol donors. Chiral amines resulting in chiral enamines can attack a Mannich acceptor, usually a prochiral aldimine, thereby introducing one or two stereocenters in the Mannich product. The catalytic cycle is completed by regeneration of the amine catalyst through hydrolysis. The products are *β*-aminoaldehydes or *β*-aminoketones, which are optionally substituted at the *α*-position.[72] Among a wide variety of organocatalysts that have been used in

the asymmetric Mannich reaction, the most widely used are proline. L-proline catalyzed Mannich reactions gives easy access to *syn*-products (**9**). Mechanistically, the stereochemical outcome of all of the reactions can be explained by involving a transition state (**8**) as depicted in (**Scheme 1.4**) The activation of imine through acidic proton of proline takes place through TS (**8**), where nucleophilic attack of *si*-face of the *anti*-enamine (**7**) *in situ* formed from ketone and proline takes place on the *si*-face of (*E*)-aldimine.[73] This model explains the stereochemical outcome of many similar reactions that have appeared in the literature.



Scheme 1.4 Proline catalyzed Mannich reaction involving enamine formation

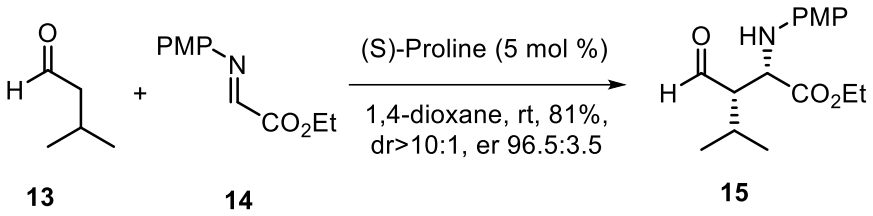
The first example of a direct organocatalytic asymmetric Mannich reaction described by B. List *et al.* can be regarded as a prototype of this kind of activation.[74] It made use of (*S*)-proline as the chiral amine in the reaction of an aldehyde, an amine, and a ketone in one pot in a reminiscence of the original Mannich concept. A *p*-anisidine (**6**) was chosen as a very reactive amine, acetone (**11**) as the nucleophile, and several different aliphatic and aromatic aldehydes were used as electrophiles. In the example given below *p*-nitrobenzaldehyde (**10**) gave the corresponding *N*-PMP-imine *in situ* and reacted to the product (**11**) under proline-catalysis in 50% yield and with excellent stereoselectivity (**Scheme 1.5**). This approach led to the development of highly enantioselective and efficient syntheses of aminocarbonyl compounds (**12**) using ketones as donors. The main advantage of the three-component procedure is that it does not require any preformed imine and enol equivalents.



Scheme 1.5 First highly enantioselective three-component direct Mannich reaction

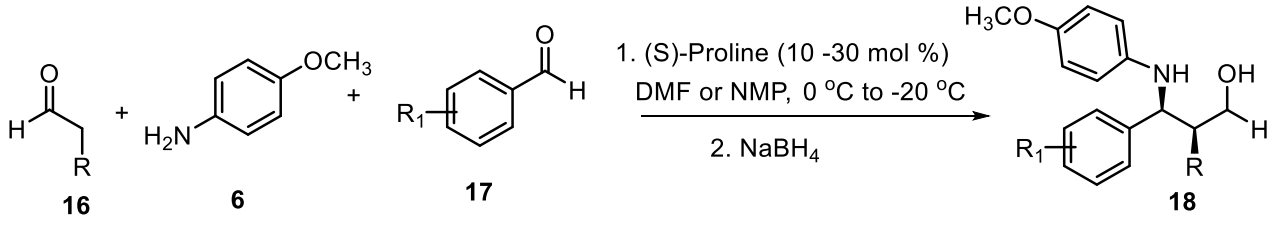
C.F. Barbas III and coworkers group made an important contribution to the development of the proline catalyzed Mannich reaction by introducing aldehydes as donors.[75] As an example, *N*-

PMP protected *α*-imino ester (**14**) was reacted with a small excess of (1.5 equiv.) of iso-valeraldehyde (**13**) to yield protected *α*-amino acid ester (**15**) (**Scheme 1.6**). 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.[76-77] These esters are direct precursors of α-amino acids.



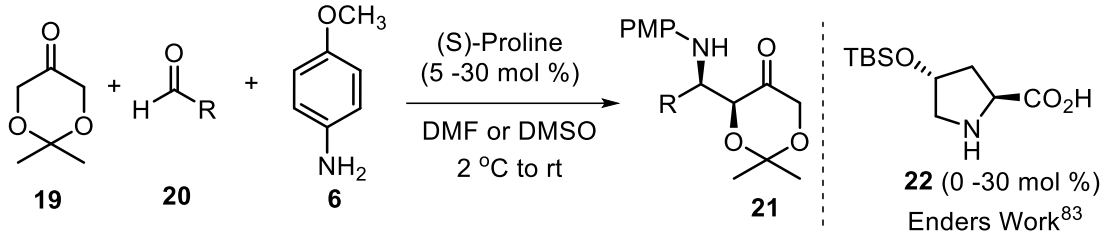
Scheme 1.6 First use of unmodified aldehydes in the proline-catalyzed Mannich reaction

The development of a three-component, proline-catalyzed cross-Mannich reaction of two unmodified aldehydes and *p*-methoxyaniline (**6**) was reported independently by the groups of Hayashi,[78] Barbas,[79] and Córdova.[80] While the three methods differ slightly, all used dimethylformamide (DMF) or *N*-methylpyrrolidinone (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 (**18**) (**Scheme 1.7**). A variety of aldehydes (**16**) could be employed as a donor. The reactions proceeded with good selectivity. Diastereomeric ratios were typical (> 95:5), and only very few examples had enantiomeric ratios (< 95:5). In addition, the reactions gave high yields (70-90%) in most cases. While aromatic aldehydes (**17**) were mostly used as acceptors, Barbas also reported the self-Mannich reaction between two aliphatic aldehydes. The products were generally formed with lower selectivities, such as diastereomeric ratios (5:1) and enantiomeric ratio's (90.5:9.5 to 93.5:6.5). The product derived from isovaleraldehyde (**18**) as the bulkiest aldehyde in this screening was formed with (59:41 er).



Scheme 1.7 Enantioselective three-component cross-Mannich reaction of unmodified aldehydes

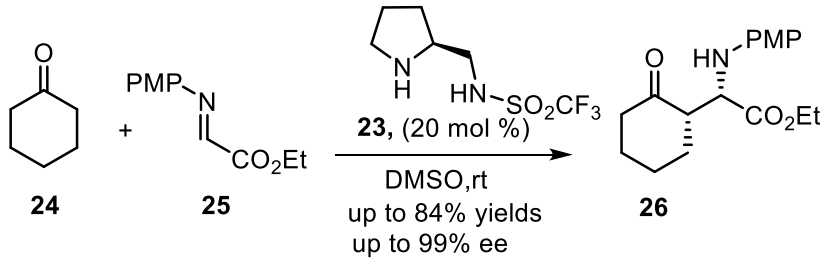
The organocatalytic entry to amino sugars *via* the Mannich reaction has been broadened by the groups of Córdova,[81] Westermann,[82] and Enders[83] with the use of protected dihydroxyacetone (**19**) (**Scheme 1.8**). The amino sugars (**21**) were typically prepared with high yields and excellent selectivity. The group of Westermann used performed imines from aldehyde (**20**), and *p*-methoxy aniline (**6**) while both Córdova and Enders developed three-component reactions. Moreover, Enders *et al*. reported TBS-protected 4-hydroxyproline (**22**) to be a superior catalyst due to the better solubility.



Scheme 1.8 Synthesis of aminoketones through Mannich reaction

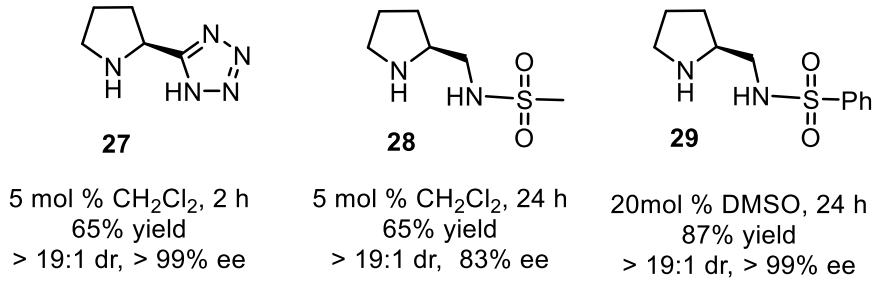
However, several researchers have been interested in finding different catalysts. List[84] and Barbas[85] have researched pyrrolidine-derived catalysts for the reaction of ketones and aldehydes in the Mannich reaction. Córdova screened acyclic amino acids such as alanine or serine, which also catalyzed the Mannich reaction with good selectivities,[86] but proline remained the catalyst of choice. This may be because of its high selectivity, easy handling, and additional advantage of being cheap and available in both enantiomeric forms.

Wang and coworkers disclosed the use of pyrrolidine-sulfonamide (**23**) as an alternative to proline.[87] As an example, it was used in the reaction of cyclohexanone (**24**) with ethyl glyoxalate imine (**25**) in protic and aprotic solvents with good yields (up to 90%) (**Scheme 1.9**). Hence, the desired *syn*-Mannich product (**26)** was obtained with high diastereo- (> 95:5) and enantiomeric ratio's (> 98.5:1.5).



Scheme 1.9 Pyrrolidine-sulfonamide as an alternative catalyst to proline

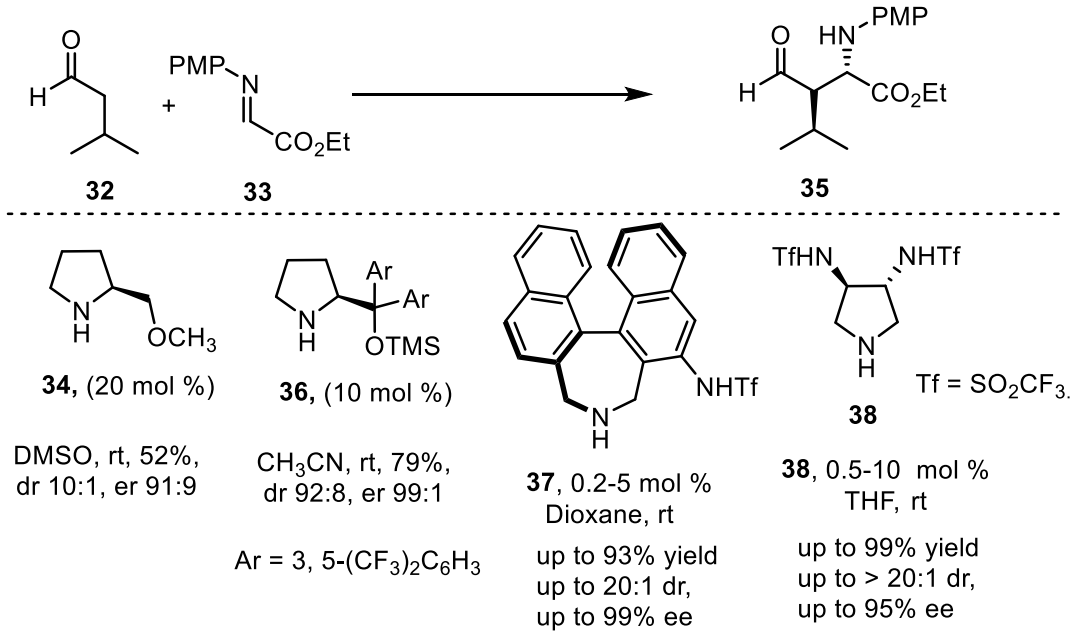
S. Ley and coworkers chose the same reaction (**Scheme 1.10**) to evaluate catalysts (**27**, **28**, and **29**) (**Scheme 1.10**).[88] This survey was mainly focused on the use of less polar solvents. While proline-catalysis is usually conducted in highly polar solvents such as DMSO or DMF due to the low solubility of proline in less polar solvents, the new catalysts were found to be efficient even in DCM or THF, and product (**26**) was obtained in high diastereo- (> 95:5) and enantiomeric ratio's (> 97.5:2.5) in most cases. It was furthermore demonstrated that even a catalyst loading (1 mol %) of (**29**) was enough to catalyze the reaction without loss of enantioselectivity.



Scheme 1.10 Improved catalysts for the Mannich reaction

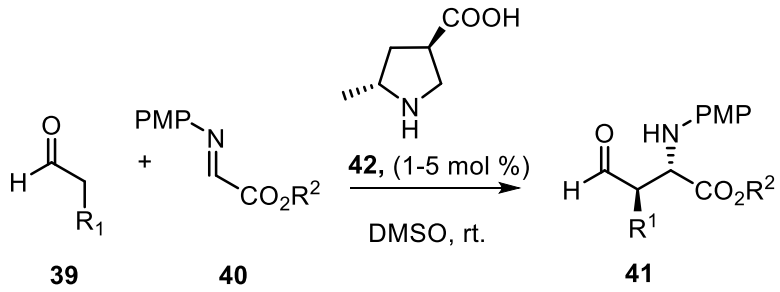
The first *anti*-selective organocatalytic Mannich reaction was published by Barbas in 2002.[89] (*S*)-2-methoxymethylpyrrolidine (**34**) (20 mol %) served as a catalyst for a reaction that is exemplified by the reaction of (**32**) and (**33**) to yield (**35**) (**Scheme 1.11**). Different aldehydes were employed in the initial screening. The diastereoselectivity was typically higher than (90:10), but when a very small aldehyde like *n*-butanal was used, it dropped to (1:1). Jørgensen's group later used *α, α*-diarylprolinol silyl ether (**36**) as a catalyst for the same reaction (**Scheme 1.11**).[90] While the diastereoselectivity was not improved much, both the yield and enantioselectivity were significantly better with (**36**). In addition, it could also be used for small, unbranched aldehydes such as propionaldehyde without significant loss of selectivity.

Maruoka introduced a new motif to chiral enamine-based catalysts with (**37**).[91] Unlike proline and its derivatives, the catalyst is based on a seven-membered ring. The chirality is derived from the BINOL-backbone. The catalyst was tested in the same reaction (**Scheme 1.11**), Catalyst (**37**) also proved to be superior with regard to the activity, as it could be used with catalyst loadings of (0.2 to 5 mol %) and produce high diastereo- (> 20:1) and enantiomeric ratio's (up to > 99.5:0.5). To obtain a more reactive catalyst for bulky aldehydes, the same group synthesized C2 symmetric catalyst (**38**).[92] Higher yields were indeed obtained, and the catalyst was also suitable to activate ketones (**Scheme 1.11**). While the diastereoselectivity remained as high as before, the enantiomeric ratio's (95:5 to 97.5:2.5) were a little lower as compared to (**37**).



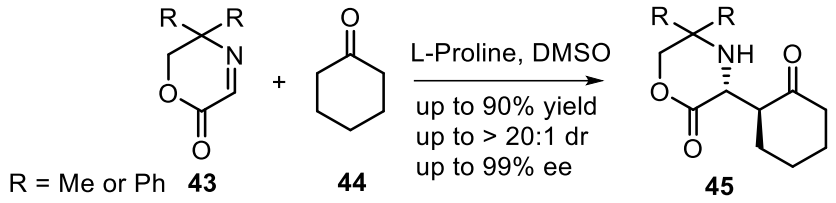
Scheme 1.11 *Anti*-selective organocatalytic Mannich reaction

From a combined effort of computational and synthetic chemistry, Barbas and Houk disclosed the highly selective catalyst (**42**)[93] for Mannich reaction between aldehydes (**39**) and *N*-PMP-imino-esters (**40**) (**Scheme 1.12**). Products (**41**) were obtained in good yields (54-92%), and excellent diastereo- (94:6 to 98:2), enantioselectivities (up to > 99.5:0.5).



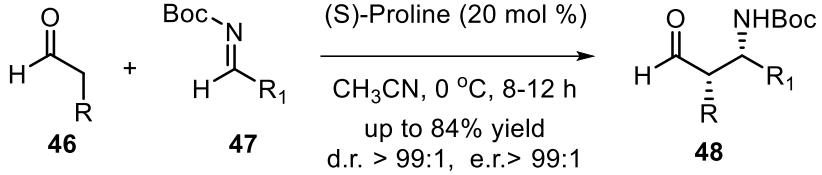
Scheme 1.12 Designer amino acid (**42**) as highly active, *anti*-selective catalyst

Glorius *et al.* developed the proline-catalyzed Mannich reaction of unactivated ketones (**44**) and demonstrated that the use of cyclic acceptors (**43**) enabled the highly stereoselective synthesis of chiral 3-substituted morpholin-2-ones (**45**) (**Scheme 1.13**).[94] These products corresponds to *α*-*D*-aminoacids that were protected at the *N*- and *O*-terminus by the diphenylethylene group. This protecting group for *α*-amino acids could be cleaved readily by hydrogenolysis in aqueous ethanol to furnish the free amino acid.



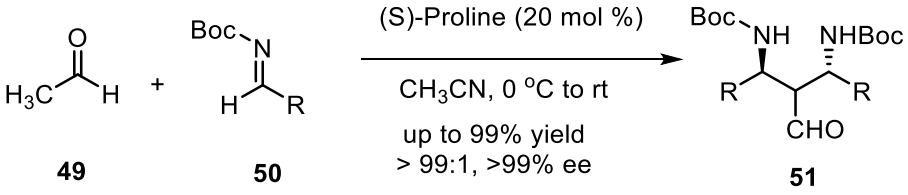
Scheme 1.13 Synthesis of chiral 3-substituted morpholin-2-ones

B. List and coworkers reported a highly diastereo- and enantioselective Mannich reaction of unmodified aldehydes (**46**) with *N*-Boc imines (**47**) using (*S*)-proline as catalyst gives crystalline β-amino aldehydes (**48**) with high yields as shown in (**Scheme 1.14**).[95] The products of this reaction typically precipitated from the reaction mixture and are useful intermediates in the synthesis of *α*-and *β*-substituted *β*-amino acids



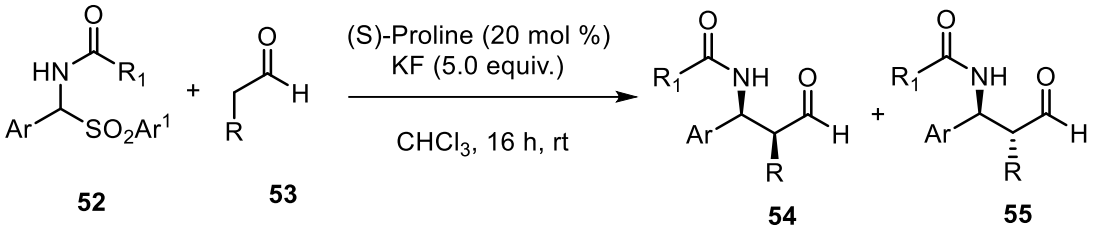
Scheme 1.14 Proline catalyzed asymmetric Mannich reaction of aldehyde and *N*-Boc-imines

List *et al*. introduced the one-pot catalytic asymmetric synthesis of pseudo-C2 *β, β'*-symmetric diaminoaldehydes with extremely high stereoselectivities, starting from acetaldehyde (**49**) and either aromatic or aliphatic *N*-Boc imines (**50**). The method was effectively extended to cross-Mannich reactions, furnishing *β, β'*-diamino aldehydes (**51**) containing three adjacent stereogenic centers (**Scheme 1.15**).[96]



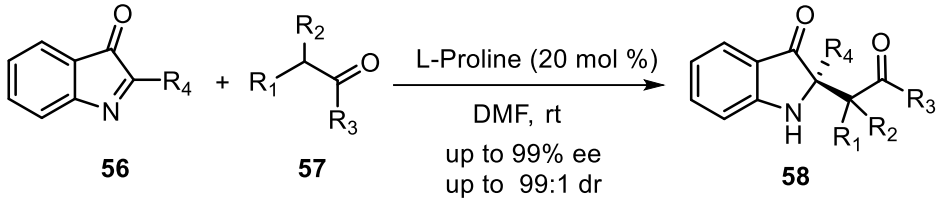
Scheme 1.15 Double Mannich reaction of acetaldehyde with N-Boc imine

In 2010, Zhao and coworkers reported the one-pot organocatalytic reactions between *α*-amido sulfones (**52**) and unmodified aldehydes (**53**) proceeded with high chemo- and enantioselectivities to furnish *β*-amino (**54** and **55**) aldehydes in high yields with up to (95:5 dr) and up to (99% ee) (**Scheme 1.16**).[97]



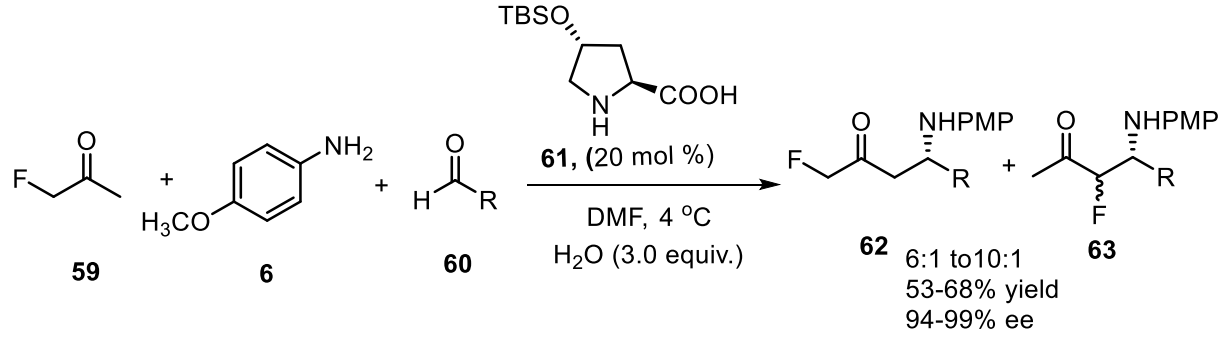
Scheme 1.16 Direct organocatalytic asymmetric Mannich reactions of **52** and **53**

In the same year, Li *et al.* developed that 2-Aryl-3*H*-indol-3-ones (**56**) reacted with aldehydes or ketones (**57**) to afford the corresponding aza-quaternary carbon addition product (**58**) in good yield with moderate to excellent regioselectivity and enantioselectivity, showed *L*-proline was an effective catalyst for the reaction.[98] The system was applied to the reaction of 2-(2-bromo-phenyl)-3*H*-indol-3-one and acetaldehyde to produce 2-[2-(2-bromophenyl)-3-oxoindolin-2-yl] acetaldehyde, which was a precursor for the synthesis of some alkaloids such as hinckdentine A (**Scheme 1.17**).



Scheme 1.17 Reaction of 2-aryl-3*H*-indol-3-ones with ketones in the presence of L-Proline

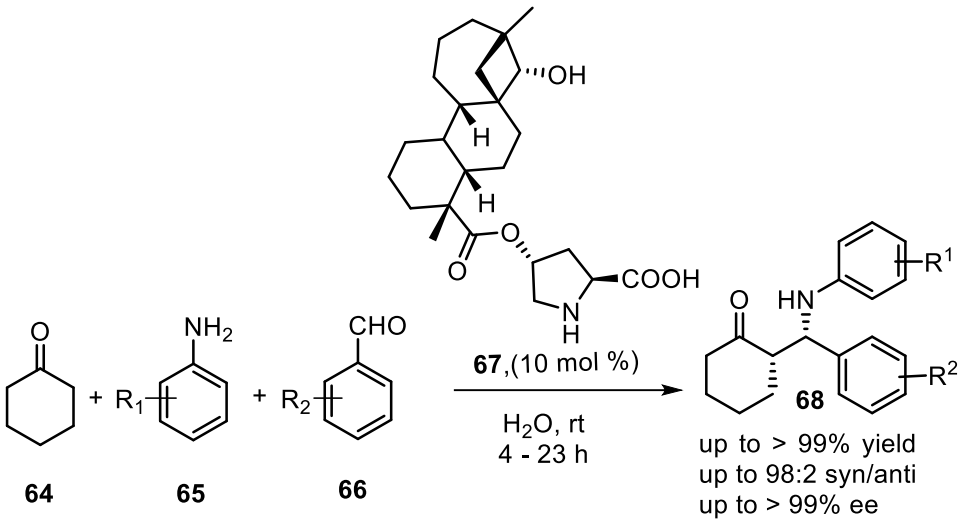
In 2011, Lu *et al.* found the direct Mannich protocol with high enantioselectivity employing fluoroacetate (**59**), *p*-anisidine (**6**), and aldehydes (**60**) catalyzed by 4-siloxyproline **(61)**, the approach allowed efficient access for pharmaceutically important fluorinated *β*-amino ketones (**62 and 63**) (**Scheme 1.18**).[99]



Scheme 1.18 Synthesis of pharmaceutically important fluorinated β-amino ketones

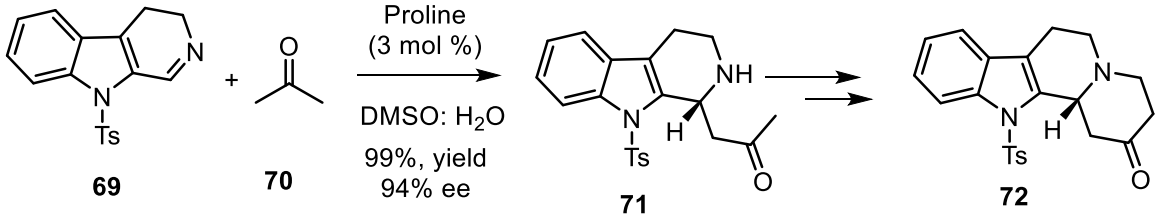
Recently, Ya-Jie An *et al.*[100] developed the asymmetric three-component Mannich reactions of cyclohexanone (**64**) and anilines (**65**) with aromatic aldehydes (**66**) in the presence of H_2O

mediated by Isosteviol–proline **(67)** as highly efficient amphiphilic organocatalysts, and afforded *syn*-Mannich products (**68**) with excellent diastereoselectivities (*syn*/*anti* up to 98:2) and enantioselectivities (up to >99% ee) (**Scheme 1.19**).



Scheme 1.19 Synthesis of *syn*-Mannich products using amphiphilic organocatalysts (**67**)

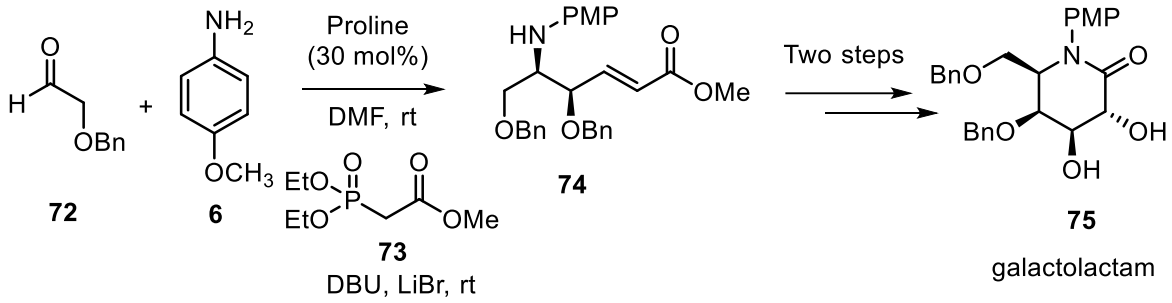
Ohsawa and coworkers reported the synthesis of addition product (**71**) from starting materials 9-tosyl-3,4-dihydrocarboline (**69**) and a ketone (**70**) in the presence of (*S*)-proline as a catalyst in good yield and high enantioselectivity as shown in (**Scheme 1.20**).[101] In the process, a small amount of water was found to affect the stereoselectivity of the products. The system was applied to reaction of compound (**69**) and ketone (**70**) to give 3,4,6,7,12,12*b*-hexahydro-1*H*-indolo-[2,3-*a*]quinolizin-2-one (**72**), which is a versatile precursor for the synthesis of some indole alkaloids.



Scheme 1.20 Reaction of 9-Tosyl-3,4-dihydro-α-carboline with acetone

Córdova and co-workers developed a stereoselective catalytic one-pot tandem reaction that involves a Mannich, Horner-Wadsworth-Emmons (HWE), subsequent Sharpless dihydroxylation sequence to provide optically active amino- and iminosugar derivatives.[102] α-benzyloxyacetaldehyde (**72**) reacted with *p*-anisidine (**6**) in presence of (*S*)-proline (30 mol %), gave the corresponding homo-Mannich product, which was treated with methyl

diethylphosphonoacetate (**73**) (2.2 equiv), DBU (2.2 equiv), and LiBr (2.2 equiv) to provide protected vicinal amino alcohol (**74**) with two stereogenic centers in good yield (64%), enantioselectivity (95%), and diastereoselectivity (4:1). Subsequent Sharpless dihydroxylation and further followed by acid-catalyzed cyclization provided the galactolactam (**75**) in good yield (74%) with enantioselectivity (95%) (**Scheme 1.21**).



Scheme 1.21 Synthesis of galactolactam involving direct Mannich reaction

1.5 Importance of nitrogen heterocycles

Diverse compounds like alkaloids, antibiotics, essential amino acids, vitamins, hemoglobin, hormones and many synthetic drugs and dyes contain heterocyclic rings as core skeletons.[103-105] Nitrogen heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. The remarkable ability of heterocyclic nuclei to serve both as biomimetics and reactive pharmacophores has largely contributed to their unique value as traditional key elements of numerous drugs constituting the main structure within a huge number of natural products and possess abroad range of biological properties.[106-107] Nitrogen heterocycles and related fused scaffolds comprise a family of biological agents with particularly interesting 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.[108-111] Because of their useful applications in the biological field, synthetic development of nitrogen heterocycles and their related fused scaffolds containing a high degree of diversity has become a leading focus in modern drug design and discovery.[112-116]

Our research group interest is to synthesize medium sized nitrogen heterocyclic ring systems. In particular this thesis is mainly concerned about the construction of five-membered nitrogen heterocycles such as pyrrolidines, pyrroles, pyrrolo-pyridazinones and their related fused natural product based scaffolds having significant importance in the current field of organic synthetic

chemistry involving the green concept of amine-catalysis. Some of the natural products containing pyrrolidine, pyrrole, and pyridazinones as core center in their structure are mentioned below in (**Figure 1.5**). [117-118]

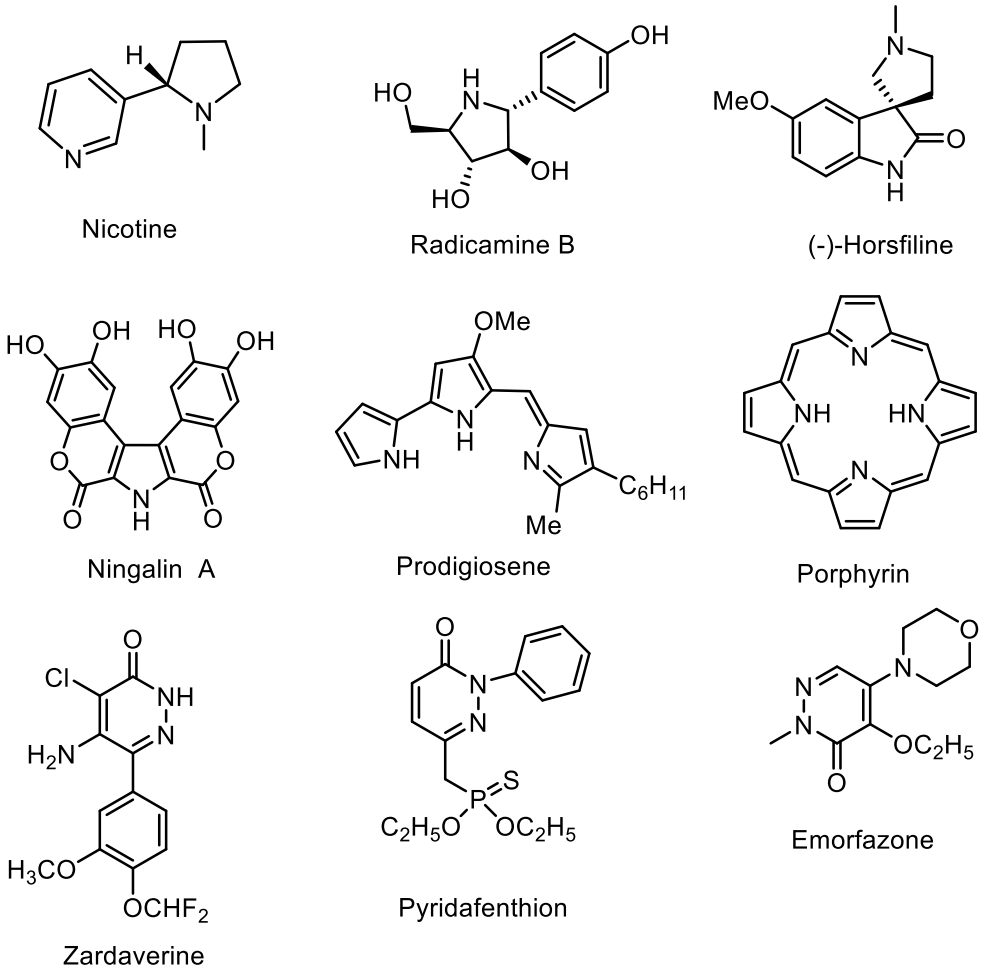


Figure 1.5 Structures of some bioactive nitrogen heterocycles

1.6 Succinaldehyde in amino-catalytic transformations

Organocatalytic domino reactions involving amine activation of carbonyl compounds have become the latest chemical technology towards the designing and development of useful synthetic methods. In this direction, linear dialdehydes such as succinaldehyde, glutaraldehyde, and other homologous compounds have attracted considerable attention as suitable substrates for amine catalyzed transformations. Due to their unique structural features, dialdehydes can be easily engaged in the creation of cascade/tandem transformations for the synthesis of valuable

natural products and drug molecules. Linear dialdehydes have been utilized for various transformations such as aldol/Mannich/Michael/Henry/Baylis-Hillman reactions in inter-and intramolecular fashion. Linear dialdehydes and their derivatives have been recognized as important substrates in the area of synthetic organic chemistry.[119] Particularly, the aim of this section is to highlight the importance of succinaldehyde which acts as 1, 3-carbon *donor-acceptor* (D-A) precursor for amine catalyzed one-pot transformations to access biologically important complex scaffolds in asymmetric as well as in non-asymmetric fashion with molecular complexity and high selectivity through amine catalysis. Amine catalyzed transformations in which linear dialdehydes are organized according to the suitability as shown in (**Figure 1.6**). Amine catalyzed transformations of succinaldehyde and other higher homologated saturated or unsaturated dialdehydes in an intramolecular fashion with various X=Y (C=C, C=N, C=O).

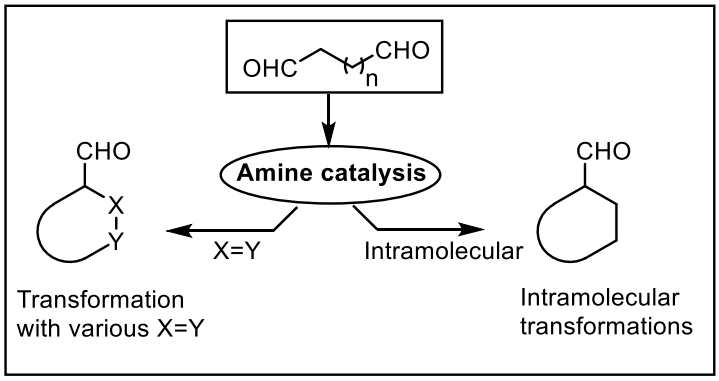
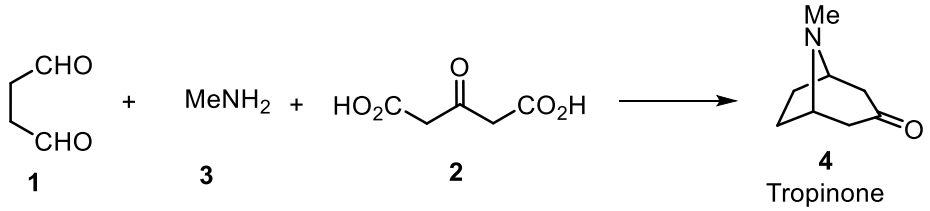


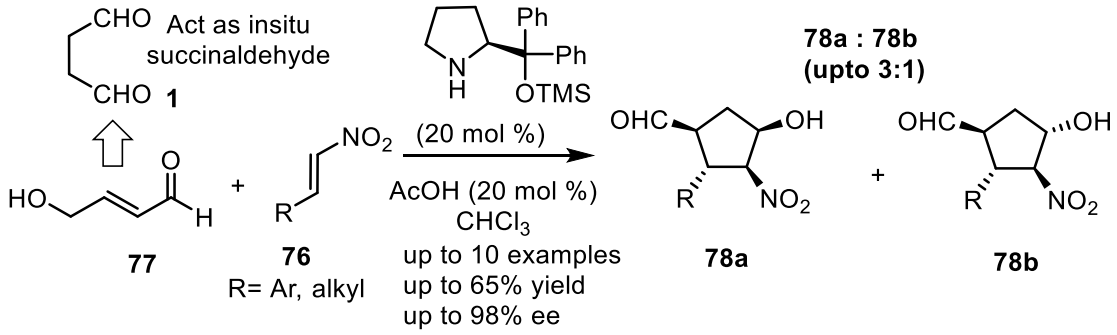
Figure 1.6 Succinaldehyde as suitable bifunctional substrate for amine-catalyzed transformations

Succinaldehyde (**1**) is a very simple 1, 4-dicarbonyl compound which undergoes polymerization in neat form, whereas reasonably stable in aqueous solution. The early utilization of succinaldehyde (**1**) to synthesize tropinone (**4**), by Sir Robinson in 1917, within a test tube is still an exciting example of total synthesis that illustrated a new way of synthetic creativity. This transformation showed the original application of dialdehydes in biogenetic-type synthesis because nature uses the identical materials to make similar compounds. This one-pot tandem strategy utilized succinaldehyde (**1**) as a valuable synthetic substrate along with amine (**3**) and acetone dicarboxylic acid (**2**) through double Mannich condensation followed by decarboxylation to furnish the bicyclic tropane skeleton (**4**) (**Scheme 1.22**).[120] In addition, succinaldehyde (**1**) has also been applied successfully for the synthesis of various heterocyclic ring systems as well as natural products.[121-123]



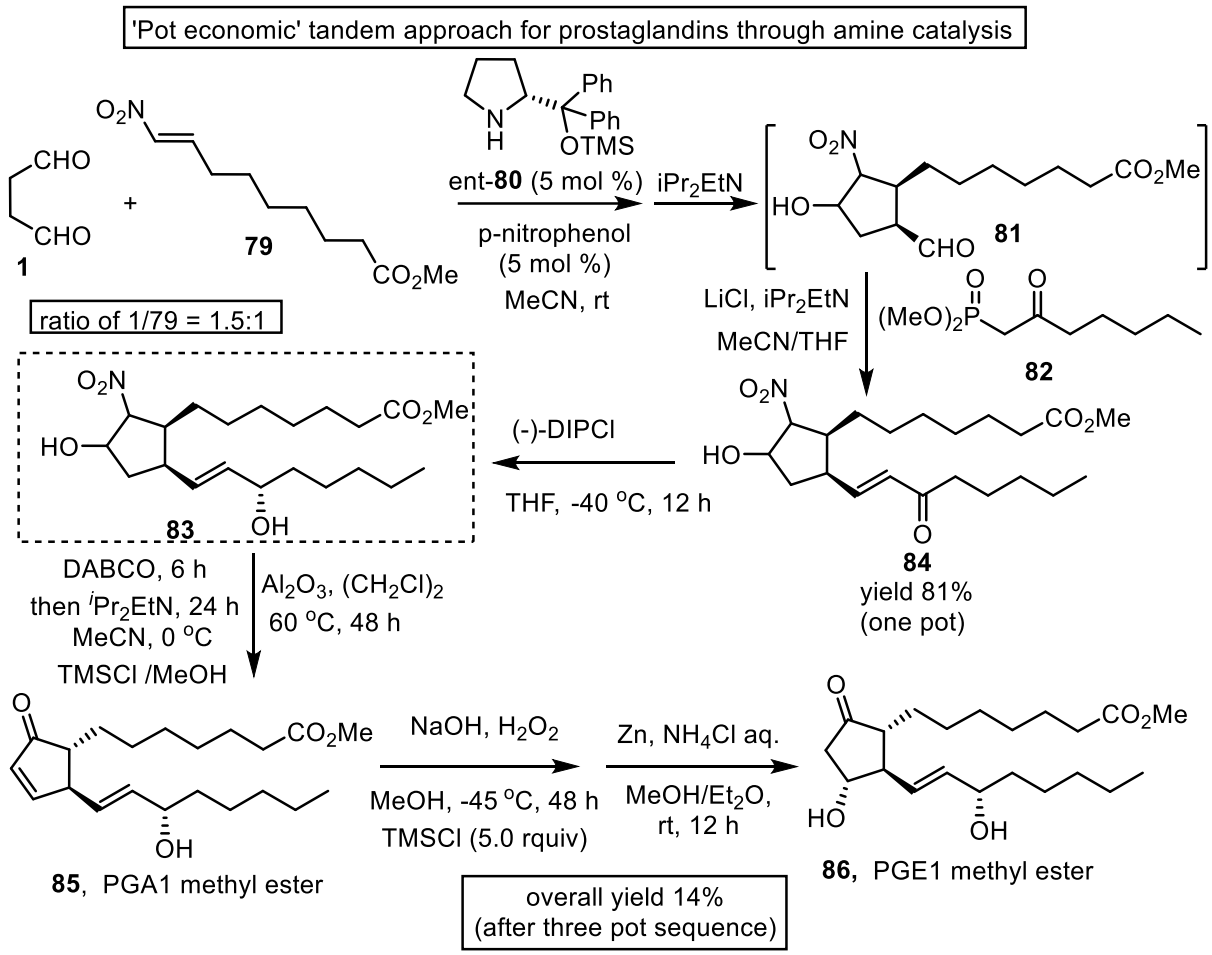
Scheme 1.22 Classical example of tropinone synthesis from succinaldehyde

In 2012, Hong and co-workers initially developed an organocatalytic [3+2] Michael-Henry cascade reaction of various nitroalkenes (**76**) with a masked dialdehyde (**77**) to synthesize cyclopentane carboxaldehyde (**78a and 78b**) decorated with four consecutive stereogenic centers with excellent enantioselectivity (up to 98%) (**Scheme 1.23**).[124]



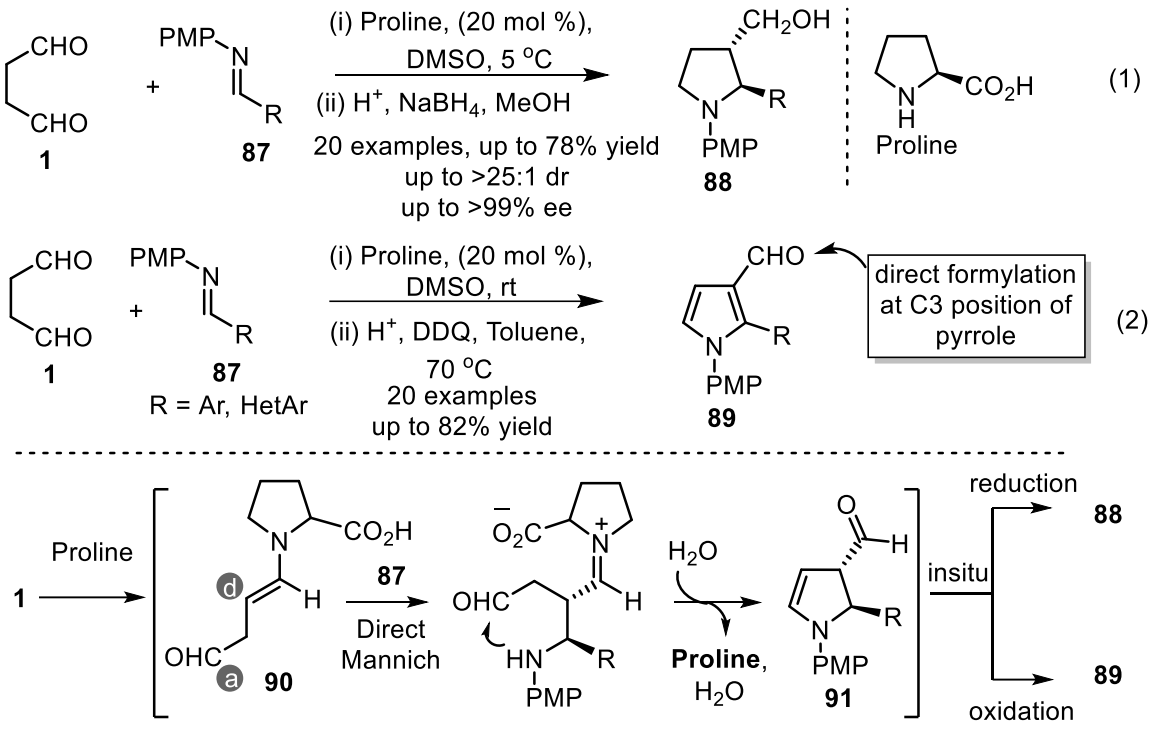
Scheme 1.23 Amine catalyzed cyclopentane synthesis using succinaldehyde surrogate

An another interesting and direct application of succinaldehyde (**1**) in amine catalyzed domino reaction through 'pot-economy' for the asymmetric total synthesis of prostaglandins was developed by Hayashi and co-workers.[125] This innovative and practical approach involved direct Michael reaction of succinaldehyde (**1**) and nitroalkene (**79**) catalyzed by diphenylprolinol silyl ether *ent*-**80** (5 mol %) followed by intramolecular Henry reaction in presence of $^{i}Pr_2EtN$, as [3+2] cycloaddition and subsequent Horner-Wadsworth-Emmons reaction as one pot transformation furnished basic prostaglandin skeleton (**83**) with high yield and selectivity. Further functional group inter-conversion from the common scaffold (**84**) with additional two-pot sequence completed the enantioselective synthesis of PGA_1 methyl ester (**85**) and PGE_1 methyl ester (**86**) in (25% and 14%) yields respectively (**Scheme 1.24**). A fascinating part of this short and efficient synthesis was not only the use of inexpensive starting materials but to also complete synthesis in just three pot sequence with few purification steps, which further reduced the amount of solvent consumption and waste production. Interestingly, one-pot operations were found to be essential due to unstable nature of intermediates and, therefore, isolation was avoided to enhance the overall yields of the process.



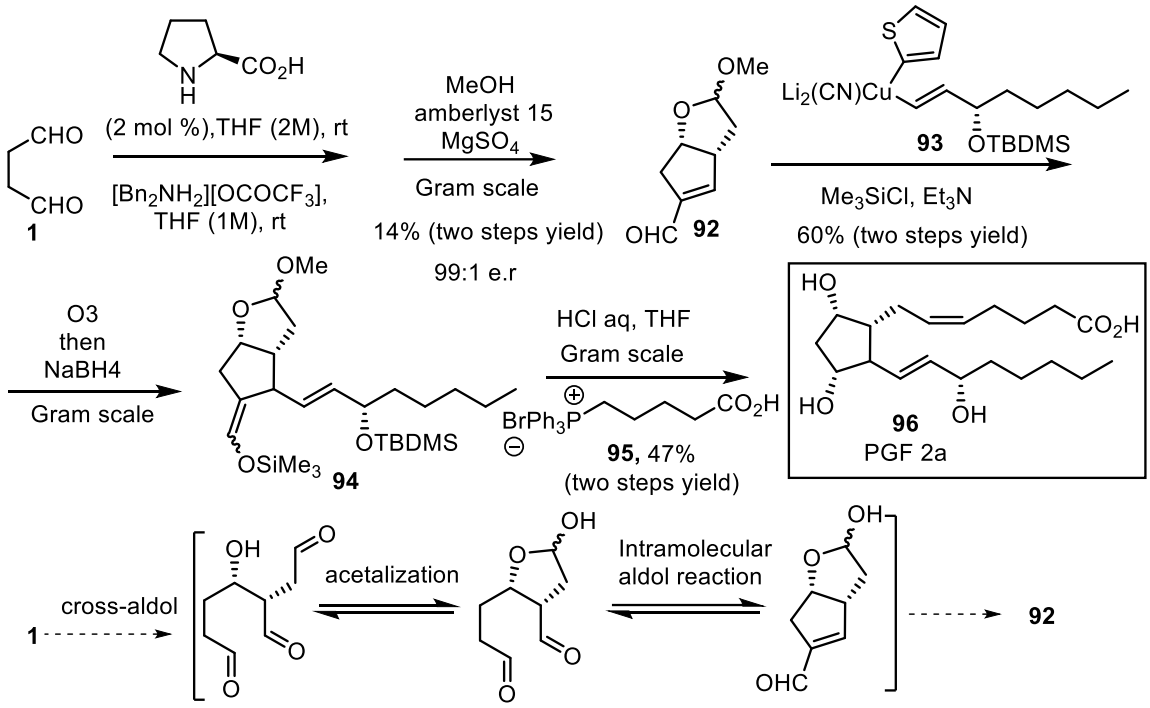
Scheme 1.24 Succinaldehyde as suitable substrate for Prostaglandins synthesis

Kumar and co-workers applied succinaldehyde (**1**) as biofunctionalized substrate for the rapid synthesis of nitrogen heterocycles through proline catalyzed cascade transformations. Initially, they developed a very simple and highly stereoselective one-pot synthesis of pyrrolidines (**88**) (**Eqn. 1, Scheme 1.25**)[126] and then first direct synthesis of substituted pyrrole-3-carboxaldehydes (**89**) as a two-step protocol was established (**Eqn. 2, Scheme 1.25**).[127] These two very similar transformations as [3+2] annulation proceed through proline-catalyzed Mannich reaction[128-129] between enamine (**90**) *in situ* generated from succinaldehyde (**1**) which serve as readily available 1,3-carbon *donor-acceptor* (D-A) precursor, and imine (**87**).The intermediate compound (**91**) was further reduced with $NaBH_4$ in the presence of acid to furnish *trans*-2,3-substituted pyrrolidine (**88**) with high yields and excellent enantioselectivities (up to >99% ee), whereas oxidative aromatization of intermediate (**91**) with DDQ produced substituted pyrrole-3-carboxaldehydes (**89**) in good to high yields.



Scheme 1.25 Synthetic strategy for pyrrolidines and pyrroles from succinaldehyde

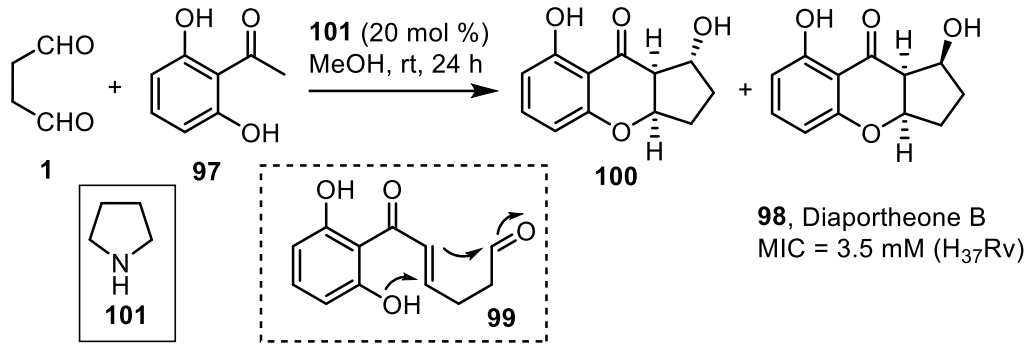
A spectacular example from Aggarwal and co-workers demonstrated the initial application of succinaldehyde in amine catalyzed cascade transformations for stereocontrolled synthesis of prostaglandin $PGF_{2\alpha}$ (**96**).[130] The key step in the synthesis involves proline catalyzed direct cross-aldol reaction of succinaldehyde (**1**) followed by intramolecular aldol condensation to give functionalized bicyclic-enal (**92**) in one step with excellent enantiomeric excess (98%). Quick access to the basic five-membered skeleton (**92**) with well placed appropriate functionality makes this method quite attractive to synthesize prostaglandin-based drugs through synthetic manipulation by installing remaining groups as shown in (**Scheme 1.26**). This gram scale and economic synthesis of $PGF_{2\alpha}$ (**96**) was completed in just six linear steps from succinaldehyde (**1**), whereas most of the earlier methods were quite lengthy, consuming more time and generating much waste.



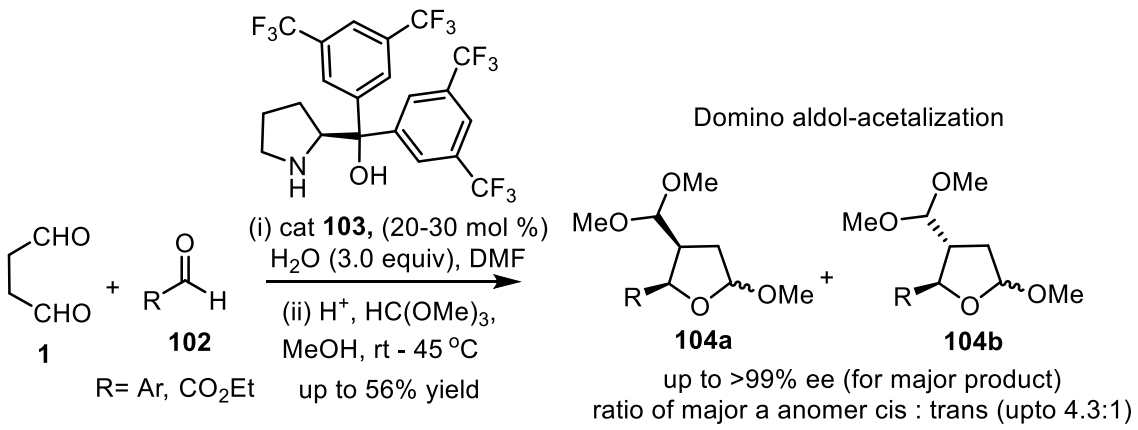
Scheme 1.26 The organocatalytic cascade strategy for Prostaglandins using succinaldehyde

Reddy and co-workers have also found the interesting application of succinaldehyde (**1**) for the synthesis of Diaportheone B (**98**) which is an anti-TB agent, through amine catalyzed process in a slightly different manner (**Scheme 1.27**).[131] The overall transformation proceeded through amine (**101**) catalyzed the condensation of 2, 6-dihydroxy acetophenone (**97**) and succinaldehyde (**1**) to a very reactive intermediate (**99**), which subsequently cyclized through domino fashion offering Diaportheone B (**98**).This one-pot process appeared as quick routes to synthesize the skeleton, however, this method suffers from low yields and selectivity. The similar application of succinaldehyde (**1**) under amine catalysis was earlier reported by Mori and co-workers for the efficient synthesis of natural products coniochaetone A and B through domino aldol/cyclization reaction.[132]

Hayashi and co-workers reported a domino approach for the asymmetric synthesis of tetrahydrofurans (**104a and 104b**) through formal [3+2] cycloaddition of succinaldehyde (**1**) with other aromatic/activated aldehydes (**102**) (**Scheme 1.28**).[133] The overall process proceeds through diarylprolinol (**103**) catalyzed direct aldol reaction of succinaldehyde (**1**) with various aldehydes (**102**), followed by an intramolecular acetal-cyclization with good yields and high enantioselectivity (up to 99%).

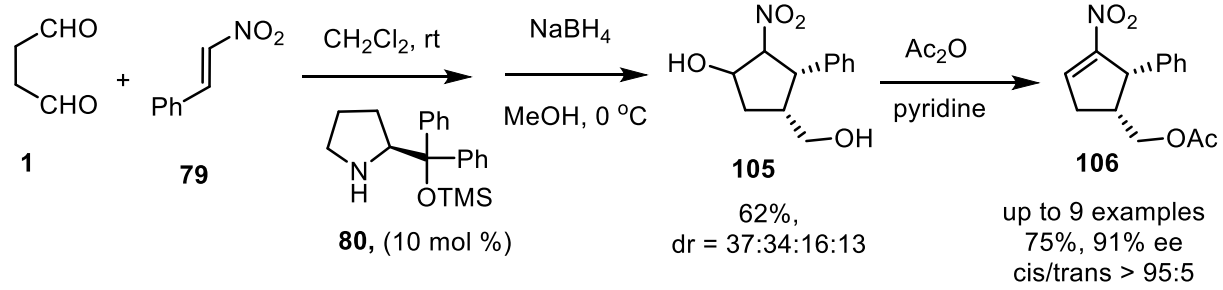


Scheme 1.27 Amine catalyzed cascade strategy for Diaportheone B involving succinaldehyde



Scheme 1.28 Amine catalyzed domino aldol/acetalization as [3+2] cycloaddition

Very recently same group demonstrated the enantioselective domino Michael/Henry reaction of nitroalkenes (**79**) with succinaldehyde (**1**) was found to proceed efficiently upon using diphenylprolinol silyl ether (**80**) as an organocatalyst. The reaction affords *cis*-disubstituted nitropentenes (**106**) with excellent diastereoselectivities and enantioselectivities after treatment of the Michael product withAc_2O and pyridine (**Scheme 1.29**).[134]



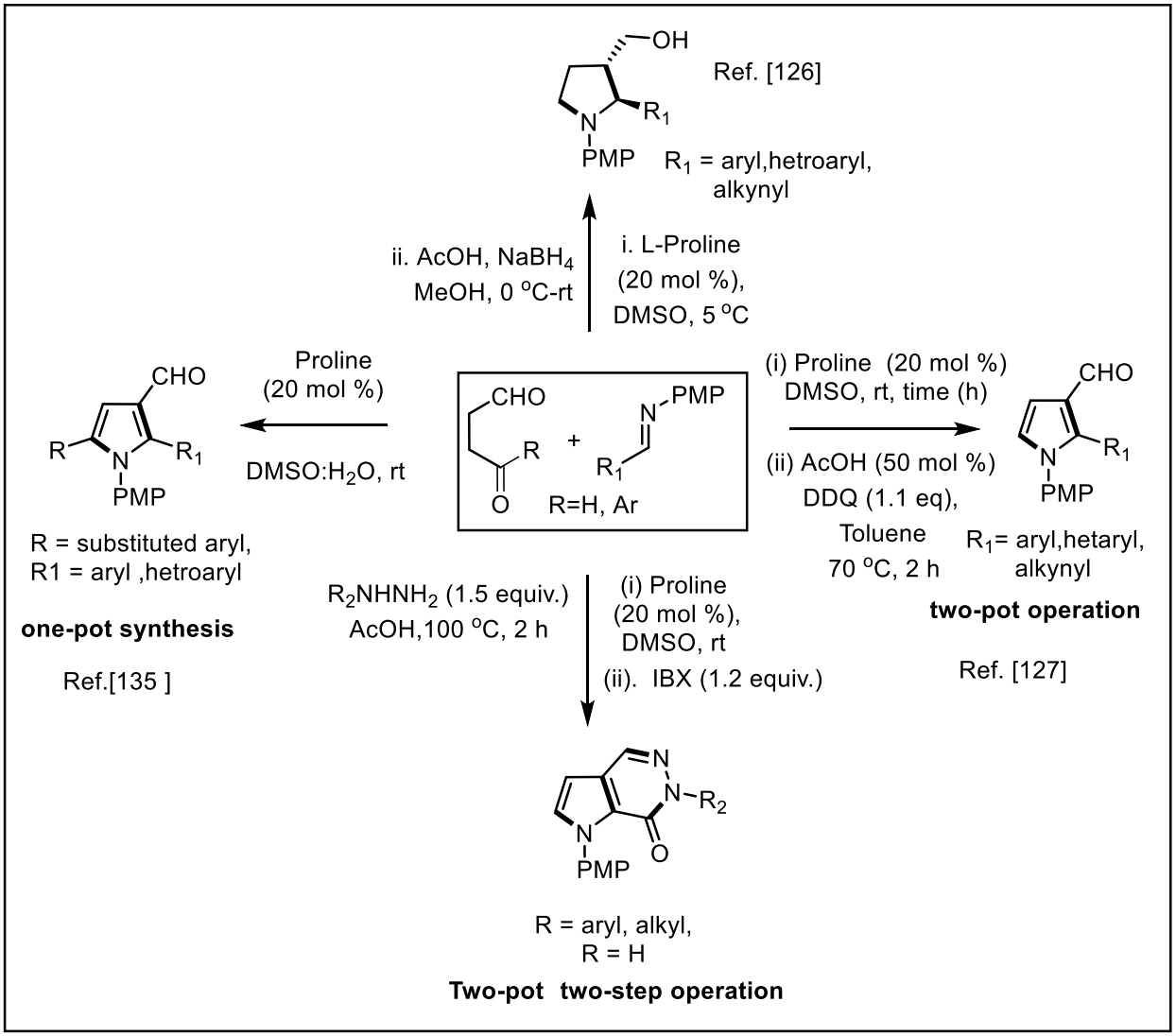
Scheme 1.29 Formal [3+2] cycloaddition of succinaldehyde with nitroalkenes

1.7 Conclusions and conception

The focus of this Ph.D. work is to expand the scope of amino-catalysis towards the synthesis of five-membered nitrogen heterocycles and related small molecule natural products (SMNPs) *via* direct Mannich-cyclization tandem reaction sequence. This chapter provides an overview in the field of organocatalysis, amine-catalysis, Mannich reactions reviewing previous work relevant to these studies and involvement of succinaldehyde in amine-catalysis. The tremendous recent development shows an augmented interest in the field of organocatalyzed direct Mannich one-pot multicomponent cascade reactions might be due to their utility in various fields, particularly in medicinal chemistry. 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 for nitrogen heterocyclic skeletons in various fields such as medicinal chemistry, material science and organometallics, more advanced methods to access these skeletons in a simple manner and obviously from readily available precursors are highly desirable. Since nitrogen heterocycles are found to have applications in diverse disciplines, syntheses of novel fused heterocyclic libraries containing highly valuable five-membered motifs are highly desirable. Therefore, the present work initiated with the use of proline-catalyst for highly enantioselective direct Mannich-cyclization sequence followed by reduction or oxidation processes towards the synthesis of substituted pyrrolidines and pyrrole based motifs. Further, the developed methodology was utilized for the synthesis of some biologically active natural products scaffolds from inexpensive and commercially available starting materials such as succinaldehyde which acts as 1, 3-carbon *donor-acceptor* (D-A) precursor and various imines.

The aim of this thesis is to discuss amino-catalyzed direct Mannich reactions, and its applications in the synthesis of five-membered nitrogen heterocyclic ring system.

In the following chapters, an overview of heterocyclic compounds and their importance, followed by the literature preceding related to the field. Further followed by the description and discussion of our own results which include synthesis of five-membered nitrogen heterocycles and related fused natural product based scaffolds in asymmetric as well as in non-asymmetric fashion using the concept of proline catalyzed domino sequences (**Scheme 1.30**).



Scheme 1.30 Brief outline for the synthesis of medium sized nitrogen heteocycles

1.8 References

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Chapter II

Proline catalyzed asymmetric synthesis of 2, 3-disubstituted pyrrolidines and related alkaloids

2.1 Introduction

Nitrogen heterocycles are probably the most representative group of organic compounds found in nature. Particularly, saturated five-membered nitrogen heterocycles such as pyrrolidines present in many important synthetic targets for chemists due to its great abundance in many bioactive synthetic and natural products.[1-4] The stereoselective synthesis of functionalized pyrrolidines is of great interest due to their significance as synthetic intermediates, as well as wide applications as chiral ligands,[5-6] nowadays from last more than one decade its great use as an organocatalysts[7-9] for a wide range of metal-mediated enantioselective protocols and increasingly present in pharmaceutical agents.[10-14]

Not surprisingly, this high value heterocyclic framework has become an attractive target for new reaction invention,[15,16] with [3+2] cycloadditions[17-22] providing elegant solutions to access stereochemically complex variants. Numerous natural product compounds containing such motifs continue to be discovered and consequently have inspired some innovative total syntheses.[23-24] For example, pyrrolidines are found fused to a tetrahydroquinoline in martinellines[25] which were isolated from the roots of *Martinella iquitosensis* and some other spiropyrrolidine-3, 3′-oxoindole alkaloids, also called spirooxindoles, known for their anti-tumor activities such as coerulescine, horsfiline, elacomine and captopril respectively used for treatment of hypertension and some other types of congestive heart failures.[26-28] Some other heterocyclic structures having pyrrolidine ring system present in their basic structure are also found in some synthetic drugs such as ramiprilan angiotensin converting enzyme (ACE) inhibitor, used for the treatment of high blood pressure and heart failure.[29] (+)- preussin an antifungal agent,[30-31] and swainsonine a potent lysosomal α-mannosidase inhibitor,[32] Hyacinthacine A4 an inhibitor of various carbohydrate possessing enzymes[33-34] and anisomycin, also mentioned as a potential psychiatric drug.[35-36]

Apart from these pyrrolidine based scaffold, Kainoids are another important class of natural nonproteinogenic amino acids which have a common characteristic structure consisting of a pyrrolidine nucleus with two carboxylic groups. They also display potent anit-helmintic properties[37]and neurotransmitting activities[38] in the mammalian central nervous system. In particular, (-)-(α)-kainic acid, the parent member of the kainoid family,[39] isolated in 1953 from the Japanese marine alga Digenea simplex,[40] has been widely used as a tool in neuropharmacology[41] for simulating central nervous system (CNS) disorders, such as

epilepsy,[42] Alzheimer's disease, and Huntington's chorea.[43] Pyrrolidines with substitution at the C2-position are important structural units in many natural products and have been found to exhibit useful biological activities such as antimicrobial, anti-inflammatory, anticonvulsant, antifungal, anticancer and antiviral as illustrated in (**Figure 2.1**)[44-47].

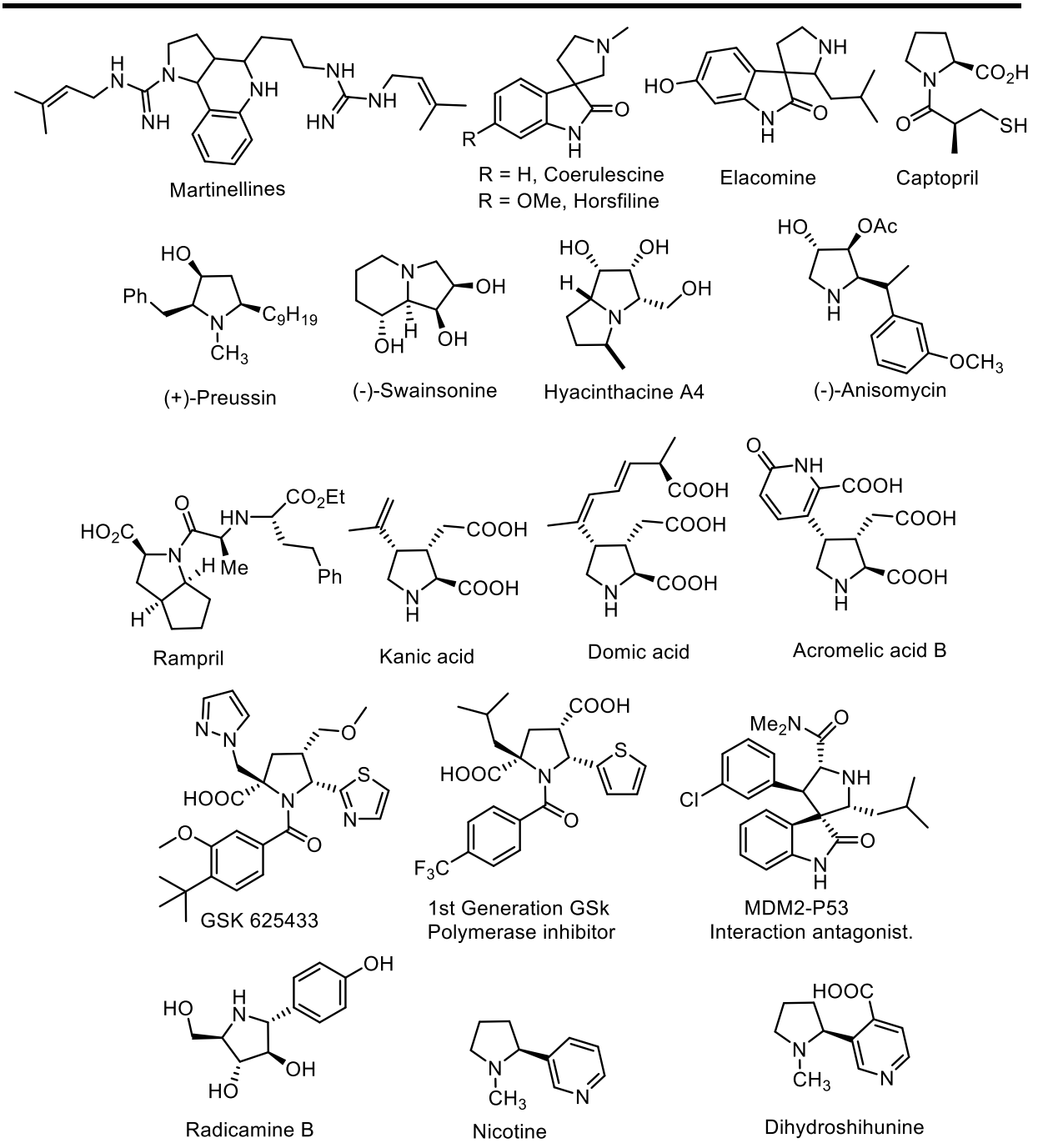


Figure 2.1 Representative natural products containing pyrrolidine ring as basic core system

2.2 Synthetic approaches of substituted pyrrolidine ring systems

In spite of the numerous strategies available in the literature for functionalized pyrrolidine synthesis, [3+2] cycloaddition reactions remains to be one of the most efficient methods for the synthesis of cyclic skeleton mainly due to '*atom-economy*'.[48-49] Conceptually, [3+2] cycloaddition/annulation methods for pyrrolidine synthesis can be described in three possible ways (**Figure 2.2**).

(**A**) 1, 3-dipolar cycloaddition between azomethine ylides (AMY) and activated alkenes (**Path A**, **Figure 2.2**).[50-56]

(**B**) [3+2] cycloaddition/annulation reaction between 1, 3-cabon-nitrogen dipolar species and alkenes (**Path B**, **Figure2.2**).[57-61]

(**C**) [3+2] cycloaddition/annulation of 1, 3-carbon *donor-acceptor* (D-A) precursor with imine (**Path C, Figure 2.2**).

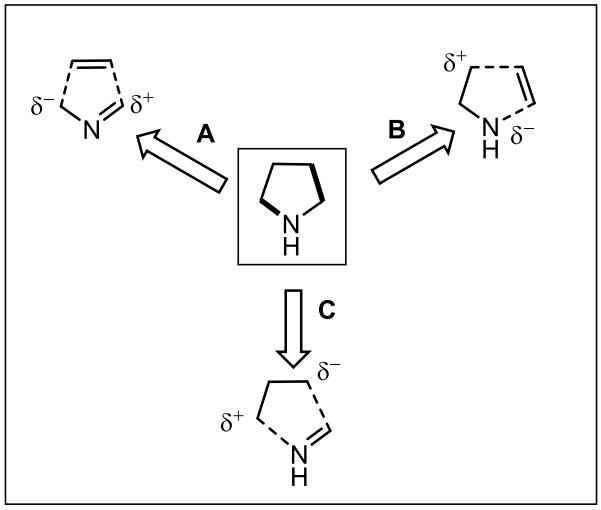


Figure 2.2 Possible routes for pyrrolidine synthesis through [3+2] cycloaddition reactions

Among the three methods, [3+2] cycloaddition/annulation through 1, 3-carbon *donor-acceptor* (D-A) strategy (Path C) with imine received less attention because of the poor availability of appropriate 1, 3-carbon dipole systems and the low reactivity of the imine counterpart. However this strategy has been well explored during past decade to synthesize pyrrolidines.

2.2.1 Path C

The main focus of this part of chapter is to provide a complete overview on alternative approach through 1, 3-carbon D-A cycloaddition/ annulation for pyrrolidine and related alkaloid synthesis

and our contribution in this direction. Importantly, the design and development of compound that possess appropriate functionalities to serve as synthetic equivalents of 1, 3-carbon dipoles still remains a challenging task and has diverse scope in organic synthesis. This approach of formal [3+2] cycloaddition/annulation of 1, 3-carbon D-A precursors with imines for the synthesis of pyrrolidines mainly rely on catalytic strategies (**Figure 2.3**) such as:

(i) Cyclopropane ring opening

(ii) Metal catalyzed trimethylenemethane

(iii) Organocatalysis

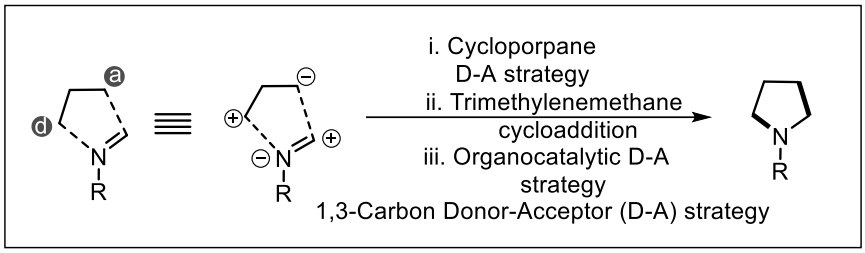


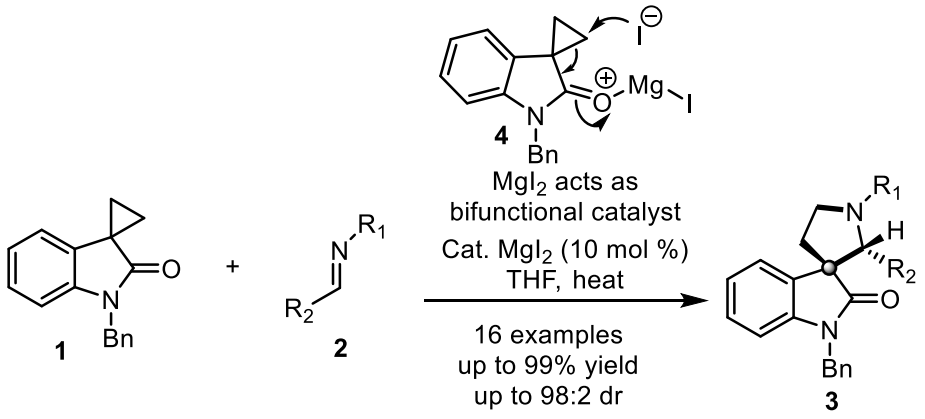
Figure 2.3 1, 3-Carbon D-A strategies for [3+2] cycloaddition/ annulation with imine

2.3 Cyclopropane D-A ring opening strategy

2.3.1 Lewis acid catalyzed ring opening of cyclopropanes

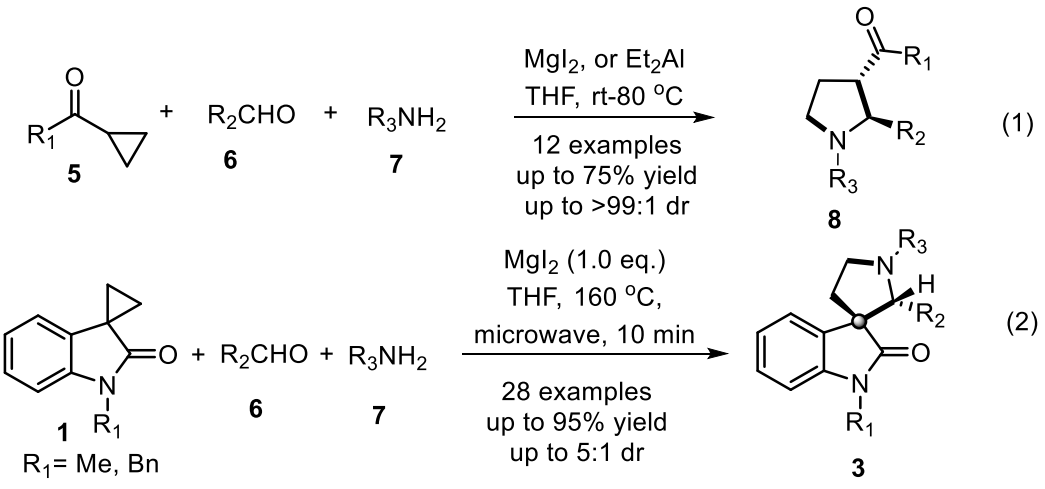
2.3.1.1 Opening of singly activated cyclopropanes

Cycloadditions through Lewis acid catalyzed ring expansion of activated cyclopropanes with imines is the most explored method in this category. The first catalytic approach for the ring expansion of singly activated cyclopropane in the formal [3+2] cycloaddition with aldimine to synthesize spiro-fused-pyrrolidine was developed by Carreira group.[62] The successful implementation of Lewis acid catalyzed ring opening of spiro[cyclopropane-1,3'-oxindole] (**1**) as *in situ* generated 1,3 carbon dipole and further reaction with imine (**2)**, provide spiro[pyrrolidine-3,3'-oxindole] ring system (**3**) with high yields and selectivity. These spiro [pyrrolidine-3,3'-oxindole] ring systems (**3**) are present in a number of compounds having biological importance. The unprecedented ring expansion is made possible by magnesium Iodide (MgI_2) which acts as a bifunctional catalyst, in which the Lewis acidity of the metal center Mg^{+2} and nucleophilicity of the counter ion I^- appear to operate in synergy as shown in (**Scheme 2.1**).



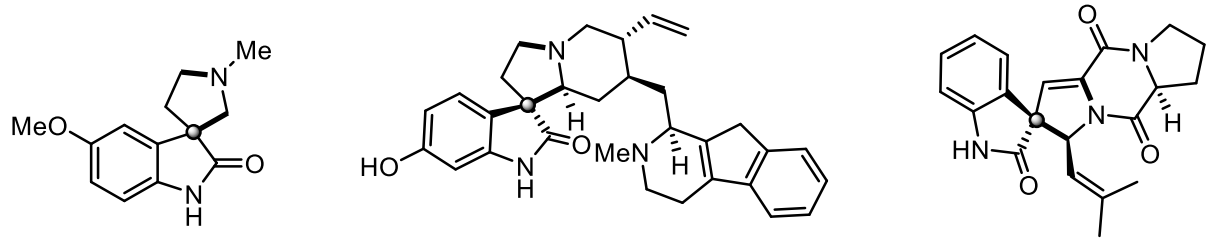
Scheme 2.1 First [3+2] annulation through MgI_2 catalysis with mechanistic presentation

Bertozzi *et al*. developed a ring expansion of various cyclopropyl ketones (**5**) with aldimines prepared *in situ* from corresponding aldehydes (**6**) and amines (**7**), under similar reaction conditions for the diastereoselective synthesis of 2,3-*trans*-pyrrolidines (**8**) (**Eq. 1, Scheme 2.2**).[63] The ring expansion of spiro-cyclopropanes (**1**) under Carreria MgI_2-protocol was further studied by Grant and coworkers under microwave conditions in employing a three component version of this strategy.[64] The rapid synthesis of a library of spiro [pyrrolidine-3,3'-oxindole] ring system (**3**) was achieved in shorter time period through stoichiometric use of MgI_2 (**Eq. 2, Scheme 2.2**).



Scheme 2.2 MgI_2 catalyzed ring expansion of cyclopropanes

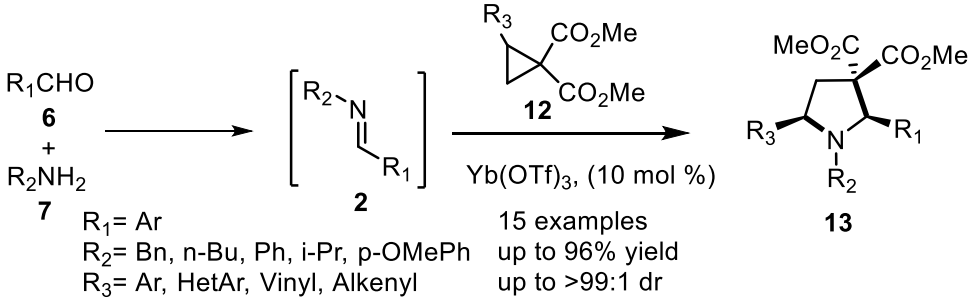
The Carreira group was successful in exploiting this synthetic strategy for the synthesis of various alkaloids such as horsfiline (**9**)[65] strychnofoline (**10**),[66-67] spirotryprostatin (**11**).[68-69] as shown in (**Scheme 2.3**).



Scheme 2.3 Some spiro-pyrrolidine based alkaloids

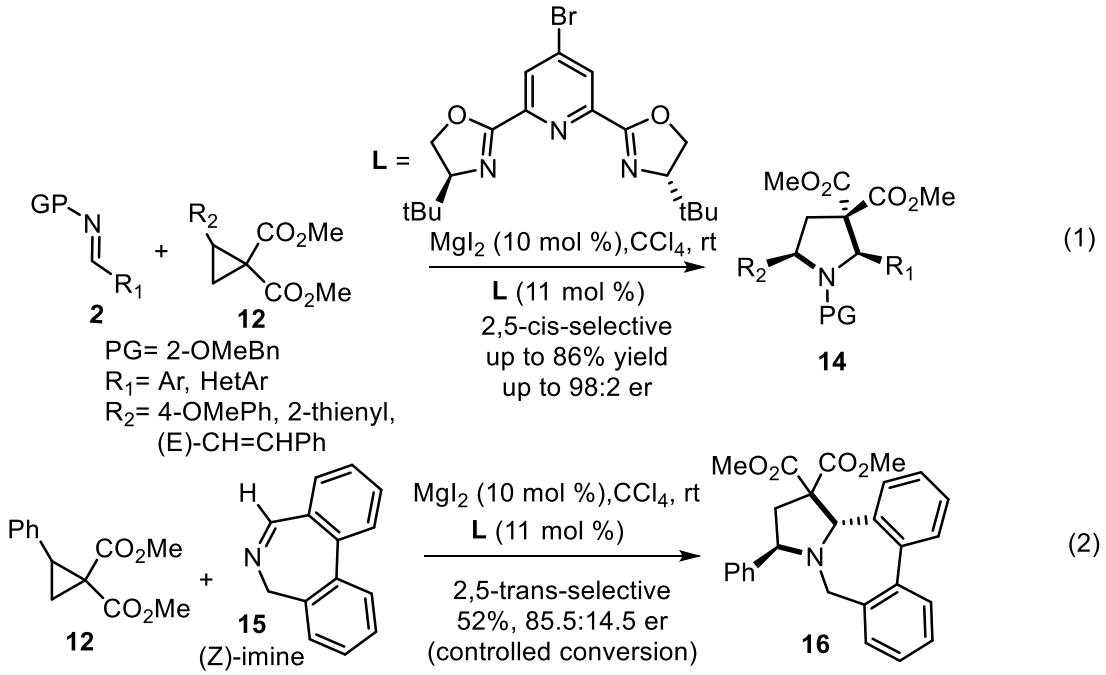
2.3.1.2 Opening of 1, 1-cyclopropanediesters

An alternative approach for the diastereoselective synthesis of densely substituted pyrrolidines through Lewis acid *viz,* $Yb(OTf)_3$ catalyzed ring opening of 1,1-cyclopropanediesters (**12**), followed by [3+2] annulation with various *in situ* generated imines (**2**) was reported by Carson and Kerr (**Scheme 2.4**).[70] Under optimized conditions, 2,5-*syn*-selective synthesis of substituted pyrrolidines (**13**) was achieved from preformed aldimines (**2**), and 1,1-cyclopropanediester (**12**). The *in situ* formation of aldimines cannot be utilized here because both aldehydes and amines are capable of undergoing reaction with activated cyclopropane under the influence of Lewis acid catalysis. Similarly, $Sc(OTf)_3$ catalyzed 2,5-*syn*-selecitve synthesis of pyrrolidines from (**12**) and various imines (**2**) was independently developed by Tang and coworkers.[71] Jones group developed the $BF_3.OEt_2$ catalyzed formal [3+2] cycloaddition between metal complex-alkynyl cyclopropanediester and imines to synthesize highly substituted pyrrolidines.[72]

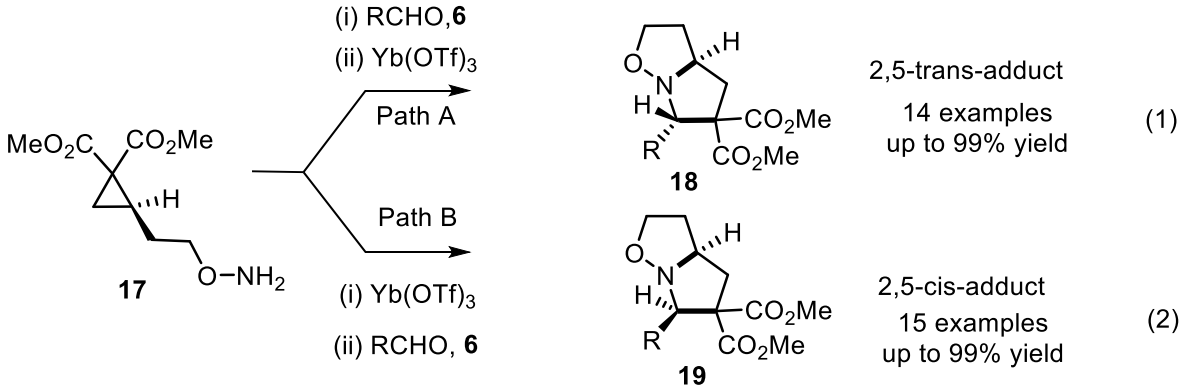


Scheme 2.4 Lewis acid catalyzed [3+2] annulation for substituted pyrrolidines

The enantioselective variant of [3+2] annulation involving ring opening D-A approach of 1, 1 cyclopropanediesters (**12**) with imines (**2**) was recently developed by Johnson and co-workers.[73] They designed the first dynamic kinetic asymmetric transformation (DyKAT) of racemic (**12**) *via* chiral Lewis acid(pybox)$_2$ MgI_2-catalyzed reaction with various (*E*)-imines (**2**) for the enantioselective synthesis of 2,5-*cis*-pyrrolidines (**14**) (**Eq. 1, Scheme 2.5**). Interestingly, alkoxy substituted *N*-benzyl protecting groups of aldimines and electron rich cyclopropane donor groups contributed towards higher yields and excellent 2,5-*cis*-selectivity, whereas low selectivity was observed in the case of 2,5-*trans*-pyrrolidine (**16**), when (*Z*)-imine (**15**) was employed under similar reaction conditions (**Eq. 2, Scheme 2.5**).



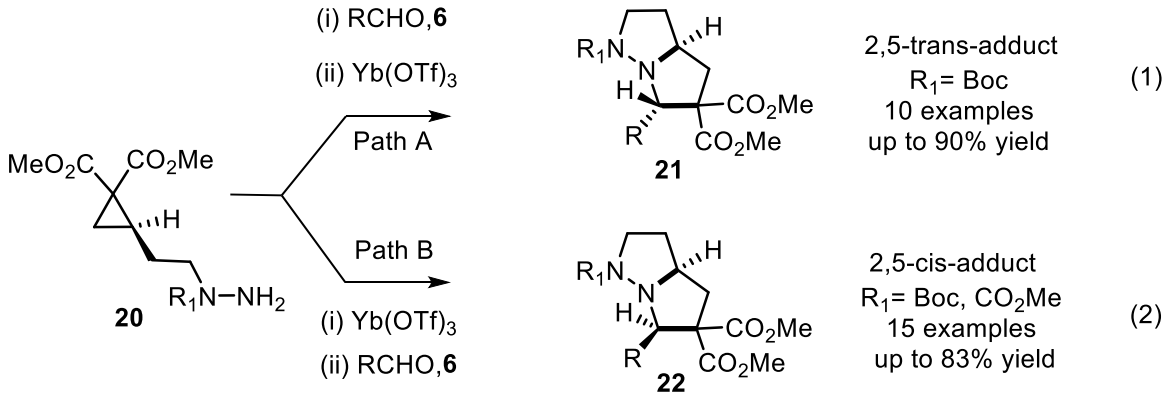
Scheme 2.5 Cyclopropane D-A [3+2] annulation in asymmetric manner



Scheme 2.6 Intramolecular cyclopropane D-A [3+2] annulation for fused pyrrolidines

Kerr group developed $Yb(OTf)_3$ catalyzed stereospecific [3+2] annulation reaction of oxime ether-tethered cyclopropanediesters for the synthesis of enantiopure pyrrolo-isoxazolidines (**18**) and (**19**), which served as precursor to the ubiquitous pyrrolidine motifs.[74] Interestingly, by simply altering the order of addition of aldehyde and catalysts to the same starting material (**17**) (**Eq. 1 and 2, Scheme 2.6**), the stereochemical outcome of the overall annulation reaction could be controlled and hence allowing easy access to functionalized enantiopure pyrrolidines with good yields.

Later on, this intramolecular [3+2] annulation strategy was further extended to the diastereoselective synthesis of complex fused bicyclopyrazolidines (**21**) and (**20**), in a very similar manner (**Eq. 1 and 2, Scheme 2.7**).[75] Either 2,5-*cis*- or 2,5-*trans*-adducts can be obtained by simply reversing the order of addition of aldehyde and catalyst to a common substrate (**20**). This intramolecular variant worked with improved reactivity as well as diastereoselectivity with a broad range of substrates allowing easy access to functionalized enantiopure pyrrolidines with high yields.



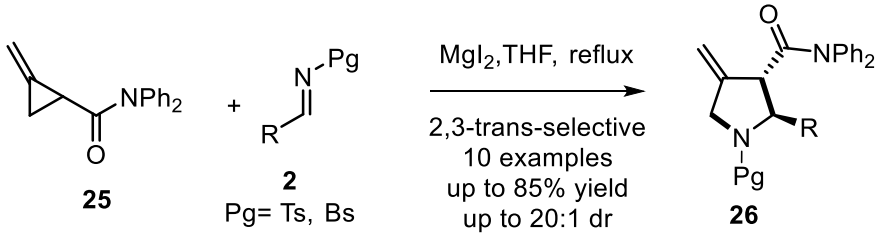
Scheme 2.7 Intramolecular cyclopropane D-A [3+2] annulation for fused pyrrolidines

Recently, Wang and co-workers extended the scope of similar 1,1-cyclopropaediester D-A strategy in intramolecular [3+2] cycloaddition with *in situ* generated imine, for the synthesis of bridged bicyclic aza-[*n*.2.1] skeletons.[76] As shown in (**Scheme 2.8**), suitably designed 1,1-cyclopropanediester (**23**), enabled two component quick synthesis of azabicyclo-[3.2.1] and azabicyclo-[4.2.1] compounds (**24**) under catalytic reaction conditions.

Scheme 2.8 Intramolecular [3+2] annulation for aza-bicyclo-[n.2.1] skeletons

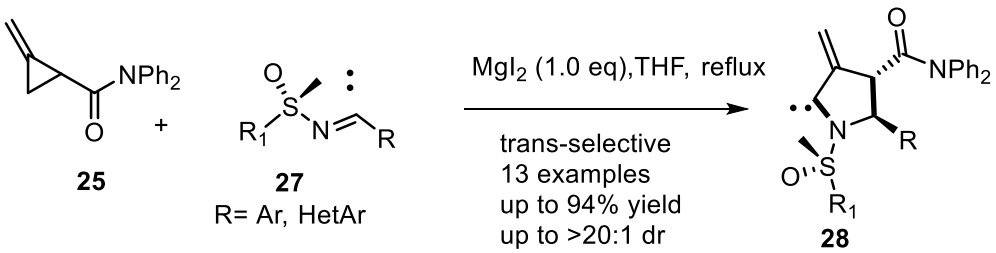
2.3.1.3 Opening of methylenecyclopropanes (MCPs)

Mono-activated MCPs being *homo*-Michael acceptors on *in situ* generation of enolate or enol intermediate, acts as nucleophiles in various [3+2] cycloaddition reactions and synthesis of heterocyclic compounds.[77] Inspired by the early report on MgI_2-mediated ring expansion of cyclopropanes from Carreira group,[78] recently Lautens and co-workers developed a novel cascade ring opening/cyclization strategy of mono-activated MCPs for pyrrolidine synthesis. In their initial efforts, tandem cyclization of MCPs-amides (**25**) with aldimines (**2**) in presence of MgI_2 was developed for methylene pyrrolidines (**26**) with high yields and *trans*-selectivity (**Scheme 2.9**).[79]



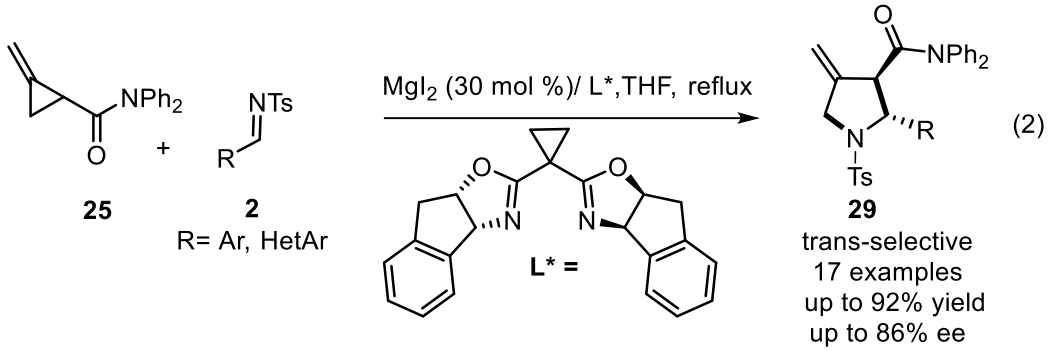
Scheme 2.9 MCP-ring opening with MgI_2 and [3+2] annulation with imines

A highly diastereoselective version of this MgI_2-mediated [3+2] annulation strategy was developed by Lautens and co-workers.[80] In this strategy, chiral aromatic sulfinimines (**27**), have been chosen based on the inference that they induce chirality for a variety of nucleophilic additions for the synthesis of methylene pyrrolidines (**28**) (**Scheme 2.10**).



Scheme 2.10 Diastereo- and enantioselective synthesis of pyrrolidines via [3+2] annulation

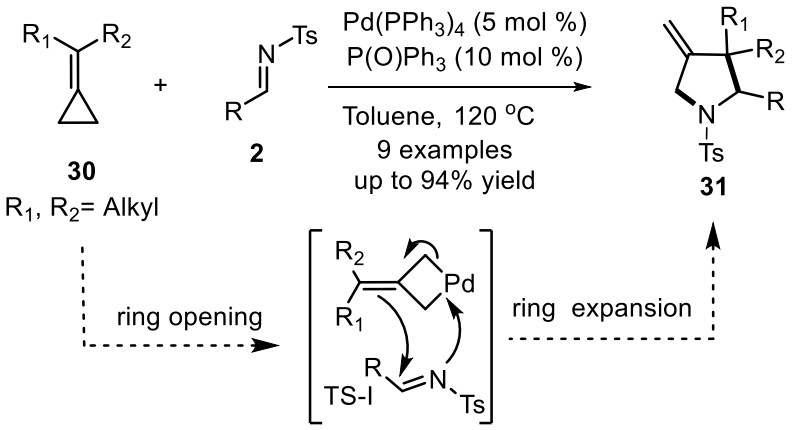
Recently enantioselective [3+2] annulation of MCPs under chiral Lewis acid-MgI_2 catalysis was achieved by the same group.[81] As depicted in (**Scheme 2.11**), ring expansion of (**25**) in presence of *N*-tosyl aldimines (**2**) using chiralbis(oxazoline) lignad-MgI_2 complex amides provided direct access to enantio-enriched methylene pyrrolidines (**29**) with high yields.



Scheme 2.11 Diastereo- and enantioselective synthesis of pyrrolidines via [3+2] annulation

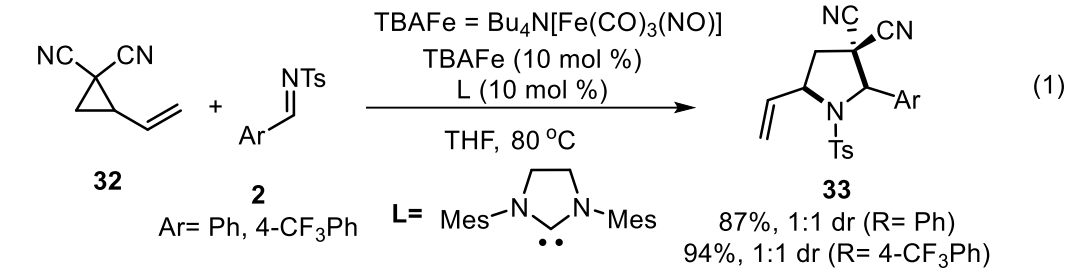
2.3.1.4 Metal catalyzed ring opening of cyclopropane

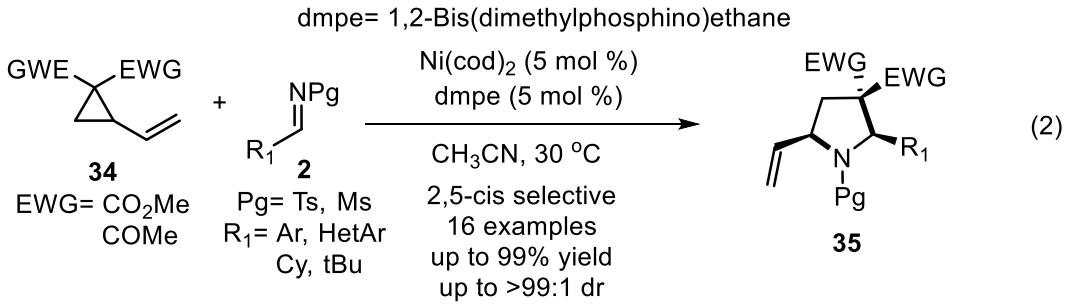
Metal catalyzed cycloaddition through the ring opening of cyclopropanes is a powerful method for the synthesis of cyclic systems.[82] However, the ring opening of cyclopropanes (D-A) under metal-catalysis followed by annulation with imine for the synthesis of substituted pyrrolidines received attention only recently. The palladium catalyzed [3+2] cycloaddition on the ring opened methylenecyclopropanes (MCPs) (**30**) with imines (**2**) reported by Yamamoto and co-workers can be considered to be the first of this kind.[83] The present atom-economical approach was explained through the reaction of (**2**) with palladacyclobutane complex (TS-I), followed by reductive elimination which furnished pyrrolidines (**31**) in high yields (**Scheme 2.12**).



Scheme 2.12 Pd-catalyzed ring opening of MCPs for [3+2] cycloaddition with imines

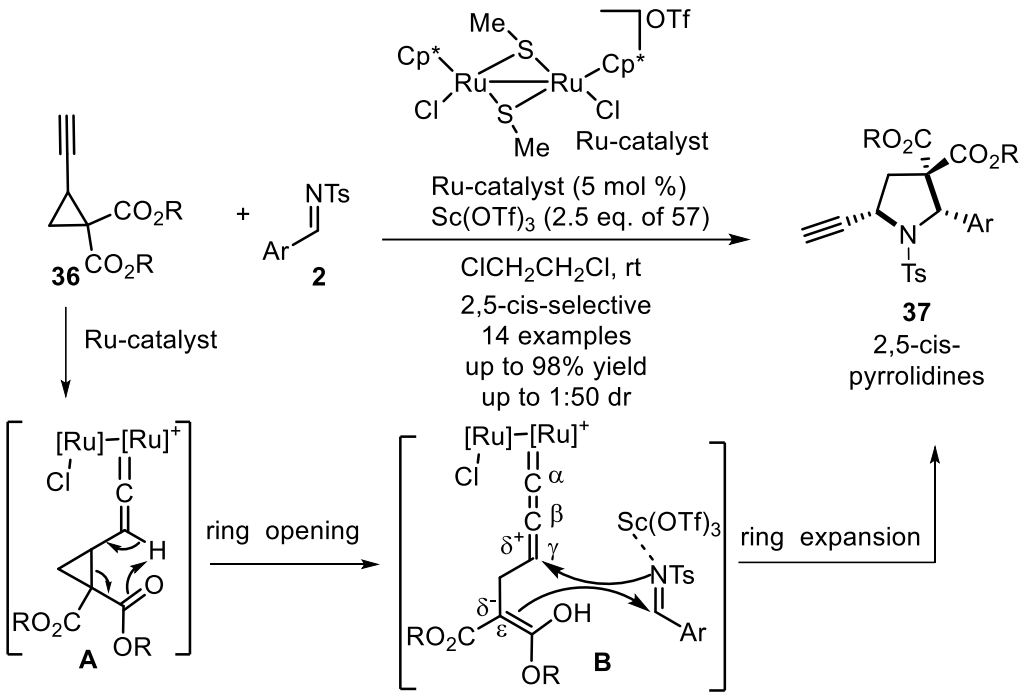
Recently, Plietker and co-workers disclosed the pyrrolidine synthesis through the iron-catalyzed ring opening of vinyl-cyclopropane (**47**), followed by [3+2] cycloaddition with imines (**2**) **(Eq. 1, Scheme 2.13**).[84] The allylic C-C bond activation with low-valent iron complex $Bu_4N[Fe(CO)_3(NO)]$ (TBAFe) through intermediate allyl Fe-complex and subsequent reaction with imines proved the synthetic utility this method for pyrrolidines (**33**). Additionally, Matsubara group also presented an analogous approach for substituted pyrrolidines (**35**) by the Nickel-catalyzed [3+2] cycloaddition between vinyl-cyclopropane (VCP) (**34**) and imines (**2**) as shown in (**Eq. 2, Scheme 2.13**).[85]





Scheme 2.13 [3+2] cycloaddition *via* metal catalyzed ring opening of vinyl-cyclopropanes

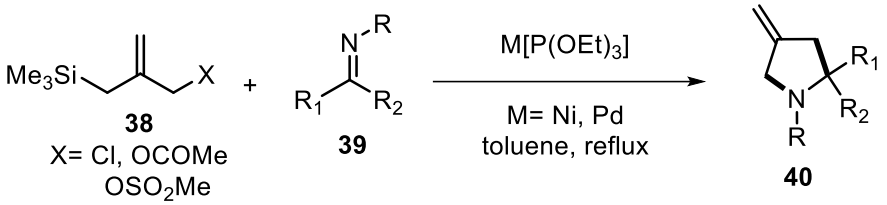
Nishibayashi and coworkers designed and developed a new ruthenium-catalyzed [3+2] cycloaddition reaction between ethynylcyclopropanes (**36**) with various aldimines (**2**) for the diastereoselective synthesis of substituted pyrrolidines (**37**).[86] Isomerization of cyclopropyl vinylidene complex **A** through ring opening process, led to the formation of corresponding metal allenylidene complex **B**, which served as a 1, 3-carbon dipolar synthon at the γ and ε positions (**Scheme 2.14**). The presence of Lewis acid $Sc(OTf)_3$ is necessary to activate the aldimines for [3+2] cycloaddition with metal allenylidene complex **B**. The [3+2] cycloaddition reaction pathway which involves the formation of ruthenium-allenylidene complex **B** as key intermediate received further support by DFT-calculations.



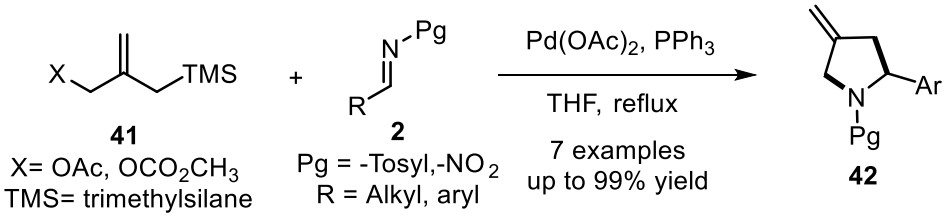
Scheme 2.14 Ruthenium catalyzed alkynyl cyclopropane for [3+2] cycloaddition

2.3.2 Metal catalyzed [3+2] cycloaddition through Trimethylenemethanes (TMMs)

Other than thermal hetero [3+2] cycloaddition of dipolar trimethylenemethanes (TMMs) developed by Nakamura group.[87-88] The first report on metal (Ni, Pd) catalyzed *in situ* generation of TMMs (**38**) followed by [3+2] cycloaddition with various imines (**39**) for one step synthesis of pyrrolidines (**40**) was presented by Jones and Kemmitt (**Scheme 2.15**).[89]



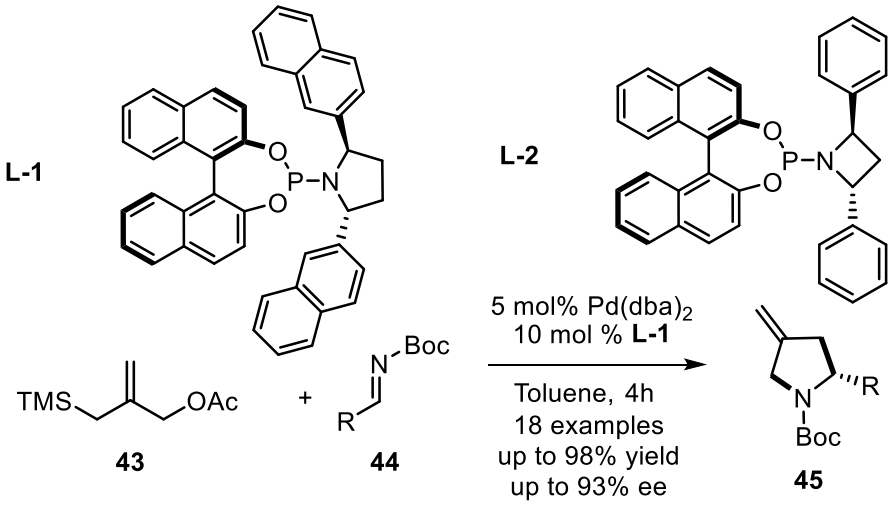
Scheme 2.15 First metal catalyzed [3+2] cycloaddition of TMMs with imines



Scheme 2.16 Pd-catalyzed [3+2] cycloaddition of TMMs

The initial success on the two steps protocol for pyrrolidine synthesis using metal catalysis was reported independently from the groups of Trost and Klummp.[90-91] Further a similar one step protocol involving cycloaddition of TMMs (**41**) with various imines was developed as detailed study in this direction.[92] Notably imines possessing an electron withdrawing group at either the carbon or nitrogen enhance the electrophilicity of imines, thus making it compatible for the reaction to occur, whereas simple imines fail to react under similar conditions. Imines (**2**) derived from aromatic aldehydes and aliphatic aldehydes work efficiently for this [3+2] cycloaddition reaction in slightly different reaction conditions with TMMs (**Scheme 2.16**).

The first catalytic asymmetric version of palladium catalyzed [3+2] cycloaddition of trimethylenemethane with imines was developed in 2007.[93] In presence of chiral phosphoramidite ligand L-1, 3-acetoxy-2-trimethylsilylmethyl-1-propene (**43**) reacted with *N*-Boc imines (**44**) to furnish pyrrolidines (**45**) in high yields and excellent enantioselectivities (**Scheme 2.17**). Having developed a practical route to the asymmetric synthesis of disubstituted *N*-Boc pyrrolidines, they turned their attention to substituted donors with the goal of preparing more complex systems.[94] Under developed conditions using electron-rich imines, a series of "normal" TMM cycloadducts were obtained with high chemo-, diastereo-, and enantioselectivities. Interestingly, the careful selection of reaction parameters such as electron-poor aldimines, concentrated reaction conditions and the use of active diphenylazetidine ligand **L-2** led to the controlled regioselective synthesis of the *exo*-cyclic product (**45**) in high yields.

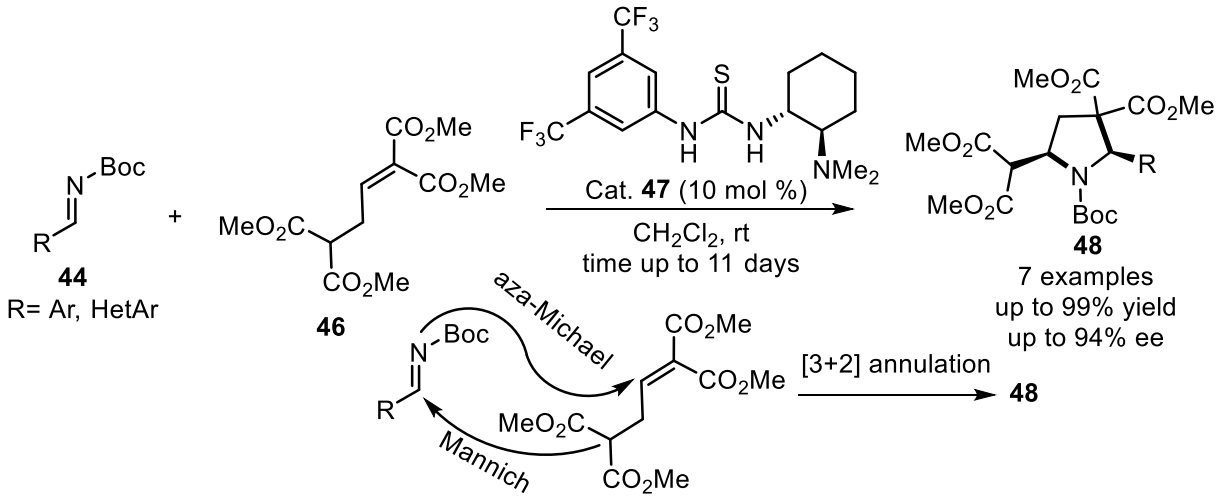


Scheme 2.17 Asymmetric and regio-selective [3+2] cycloaddition for substituted pyrrolidines

2.3.3 Organocatalytic D-A [3+2] cycloaddition/annulation strategy

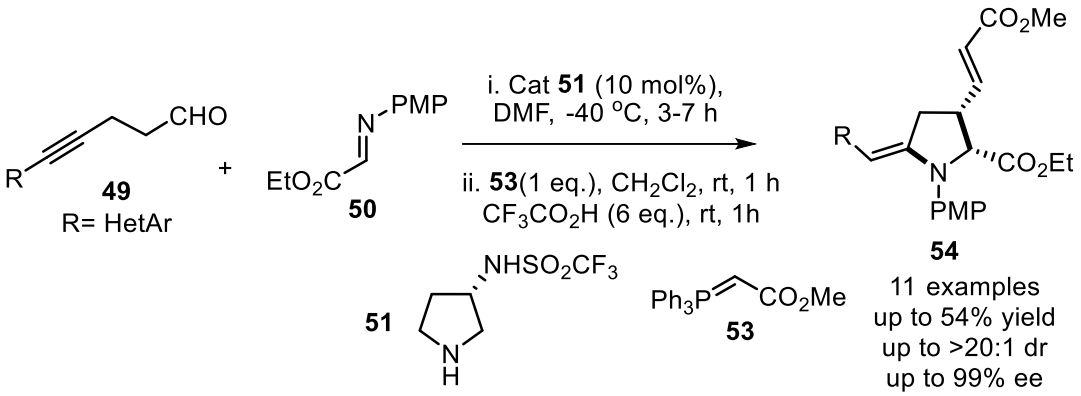
The development of organocatalysts has greatly changed the art of organic transformation in the in the past decade. The organocatalytic cascade reactions involving two or more selective transformations using single/multiple catalysis are now considered to be the most effective ways to design new catalytic asymmetric synthetic routes.[95-97] These reactions provide an easy way for the asymmetric synthesis of biologically active molecules and natural product motifs. Recently, organocatalysis has contributed for the asymmetric synthesis of functionalized pyrrolidines through *in situ* generation of suitable 1, 3-carbon D-A precursor. In this section, organocatalytic cascade strategies particularly formal [3+2] cycloadditions/ annulations with imines will be discussed.

Enders and co-workers developed the first one-pot sequential domino Mannich/aza-Michael reaction of *γ*-malonate-substituted *α, β*-unsaturated esters (**46**) with *N*-Boc arylaldimines(**44**) *via* [3+2] annulation for the synthesis of substituted pyrrolidines.[98] This new method catalyzed by bifunctional thiourea (**47**) furnished 2, 5-*cis*-configured polysubstituted pyrrolidines (**48**) in excellent yields and enantioselectivities, however, required long reaction time (**Scheme 2.18**).



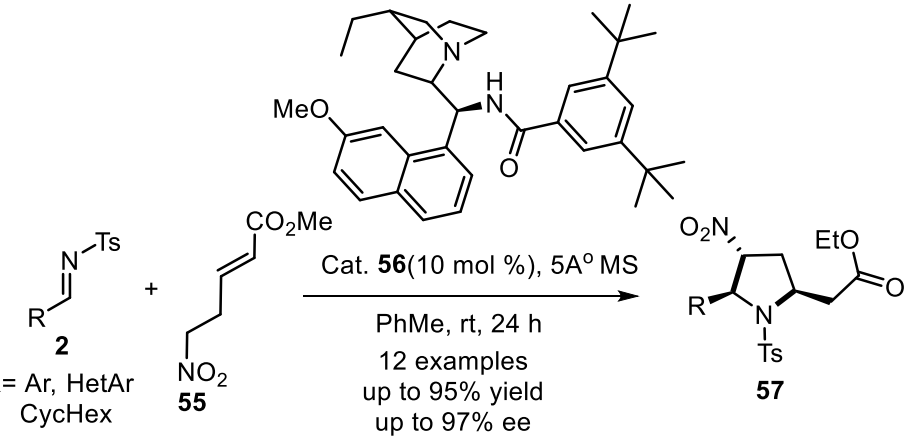
Scheme 2.18 Sequential Mannich/aza-Michael addition as [3+2] annulation reaction

De Paolis and co-workers recently developed another one-pot sequence of organocatalytic transformations for the synthesis of heteroarylmethylene-substituted pyrrolidines.[99] This reaction involved the *anti*-Mannich coupling of *N*-heteroarylalkyne aldehydes (**49**) with aldimine (**50**), followed by metal-free hydroamination *via* formal [3+2] annulation to deliver highly functionalized pyrrolidines (**54**) with very high selectivity (**Scheme 2.19**).



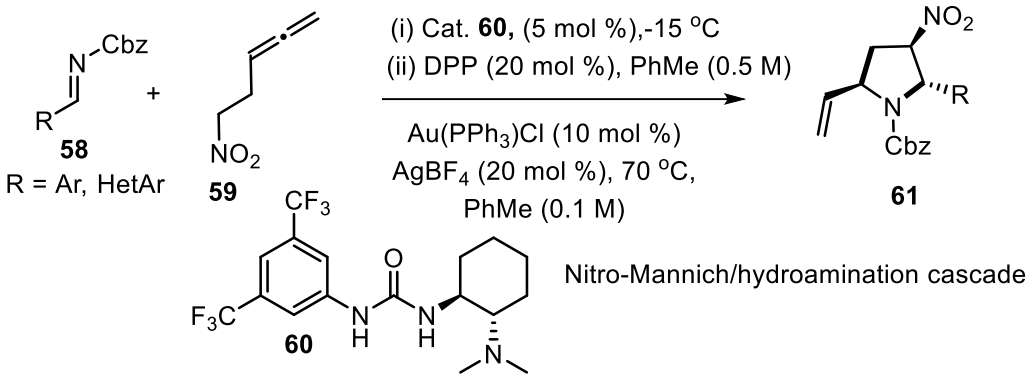
Scheme 2.19 Direct Mannich-metal free amination as [3+2] annulation for pyrrolidine

Cinchona alkaloid-derived organocatalyst (**56**) have recently been utilized by Huang and co-workers for the efficient synthesis of highly functionalized pyrrolidines (**57**), with up to three stereogenic centers in high yields and enantioselectivities.[100] The [3+2] coupling of (**2**) with (**55**) involves a reversible *aza*-Henry reaction with a dynamic kinetic resolution (DKR)-driven *aza*-Michael cyclization (**Scheme 2.20**).



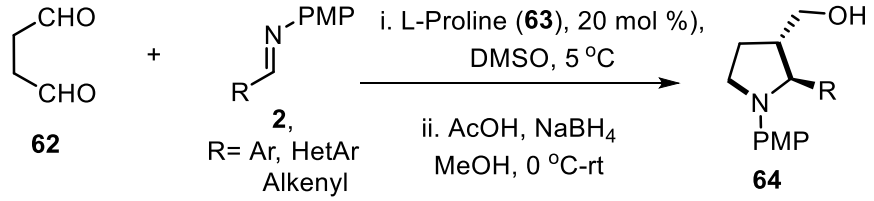
Scheme 2.20 *Aza*-Henry and DKR *aza*-Michael cascade reaction for pyrrolidine synthesis

Dixon and co-workers reported a very similar diastereoselective base-metal catalyzed one-pot nitro-Mannich/hydroamination cascade strategy for substituted pyrrolidine synthesis.[101] Very recently, the same group developed an asymmetric version of this cascade reaction for the synthesis of substituted pyrrolidines bearing three stereocentres.[102] The combination of bifunctional organocatalysis (**60**) and gold catalysis used in conjunction with *N*-Cbz imines (**58**) afforded pyrrolidines (**61**) in good yields with excellent enantioselectivities (**Scheme 2.21**).



Scheme 2.21 Organocatalyzed nitro-Mannich and gold-catalyzed hydroamination annulation

Kumar *et al.* investigated a very simple and highly stereoselective organocatalytic method for the synthesis of substituted pyrrolidines (**64**) from succinaldehyde (**62**) and *N*-PMP aldimines (**2**).[103] The [3+2] annulation method involved, L-proline (**63**) catalyzed direct Mannich reaction between imine (**2**) and succinaldehyde (**62**) which serve as readily available 1,3-carbon D-A precursor, followed by acid catalyzed reductive cyclization (**Scheme 2.22**). This one-pot cascade protocol worked under mild conditions with a wide variety of aldimines which in turn provided a true platform for the quick access of *trans*-2, 3-substituted pyrrolidines (**64**) with high yields and excellent enantioselectivities.



Scheme 2.22 Direct Mannich-reductive [3+2] annulation for substituted pyrrolidines

2.4 Results and discussion

As a part of our interest in the development of synthetic methods for heterocyclic compounds, we anticipated that succinaldehyde (**62**), a synthetically useful 1,4-dicarbonyl unit, might be explored as *in situ* generated 1,3-dipole and further formal cycloaddition with imines (**2**). This reaction involves the direct Mannich reaction and intramolecular reductive cyclization in one pot operation, as formal [3+2] cycloaddition. The initial screening of catalyst, solvents, temperature with *N*-PMP aldimine (**2c**) preformed from *p*-nitrobenzaldehyde as model substrate was investigated and summarized in (**Table 2.1**).

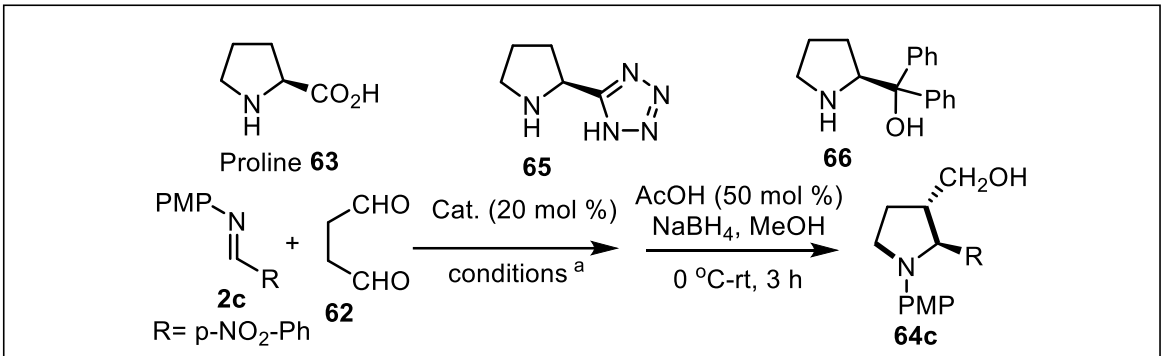
The initial experimentation showed that among the amine catalysts screened (**entry 1-3, Table 1**), proline catalyzed the direct Mannich reaction of aqueous succinaldehyde (**62**) with imine (**2**), followed by acid catalyzed reductive cyclization as one-pot cascade, afford substituted pyrrolidine (**64c**) with good yield and selectivity (**entry 1, Table 2.1**). Solvent screening (**entry 4-7, Table 2.1**) suggested the DMSO/MeOH were optimal for this two-step cascade process. Gratifyingly, enhancement in the yield (78%) and enantioselectivity (96%) observed, when this reaction was carried out at 5 ^{o}C and with 3 M sol. of succinaldehyde (**62**) (**entry 9, Table 2.1**). The positive impact of water on organocatalytic direct Mannich reaction have been discussed earlier by Barbas and others.[104-110] Furthermore, by decreasing the temperature (**entry 10, Table 2.1**), succinaldehyde concentration (**entry 11, Table 2.1**), and catalyst loading (**entry 12, Table 2.1**), led to the prolonged reaction with reduced yield due to the lability of imine in the presence of water. The reaction could not deliver the desired product when acid was not employed shows the necessity of acid to accelerate the reductive cyclization step (**entry 13, Table 2.1**). Thus, we preferred to perform this one-pot two steps cascade sequence with optimized condition (**entry 9, Table 2.1**).

With the identification of the optimal conditions, the generality of this proline (**63**) catalyzed asymmetric [3+2] annulation was examined using a variety of preformed aryl or hetero-aryl *N*-PMP aldimines (**2**) and succinaldehyde (**62**). The results are summarized in (**Table 2.2**). All of the reactions progressed smoothly to give corresponding product (**64**) in moderate to high yield's (up to 78%) with high diastereo- (> 25:1) and excellent enantioselectivity's (up to > 99% ee) under optimized conditions (**Table 2.2**). In case of electron-deficient arylimines reactions proceeded well (**entry 1-18, Table 2.2**), however the reactions were rather slow in cases of imines preformed from 2-substituted benzaldehydes (**entry 1, 4, 7, 10, 16, Table 2.2**) and naphthaldehydes (**entry 20-21, Table 2.2**) cause lower yields, perhaps because of the steric crowding. Not only aryl imine (**entry 19, Table 2.2**) but hetero-aryl imines too resulted products in high yields and high enantioselectivity (**entry 22-27, Table 2.2**). In case of alkenyl imine (**entry 28, Table 2.2**), reaction was sluggish and continued with slight low yields, while electron-rich arylimine (**entry 31, Table 2.2**) and *in situ* generated alkyl imine (**entry 32-33, Table 2.2**) failed to deliver the desired products, may be because of their less reactivity.

The structures of all the synthesized molecules of substituted pyrrolidines (**64a-64ag**) was characterized by various spectroscopic analysis such as ^{1}H NMR, ^{13}C NMR, IR, polarimetry for

optical rotation, HRMS mass spectroscopy, HPLC analysis for enantiomeric excess and further by X-ray analysis. The coupling constant determination at C2 ($J_{2H} \leq 5.5$ Hz) by ^{1}H-NMR technique confirmed the relative *trans*-stereochemistry at C2 and C3 for all products.

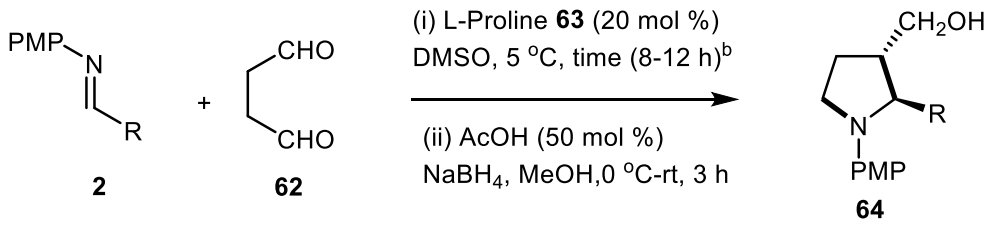
Table 2.1 Optimization of reaction condition for the synthesis of **64c**[a]

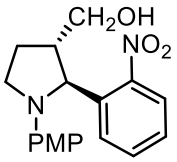
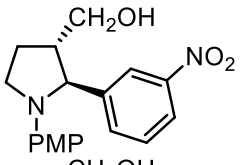
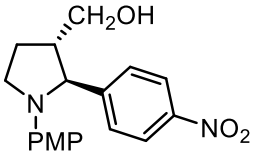
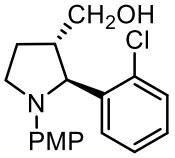
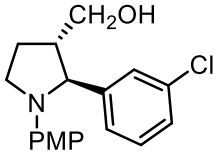
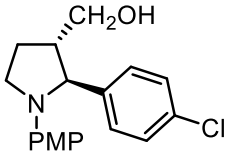
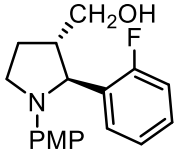
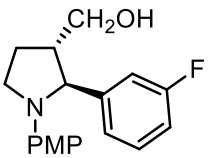


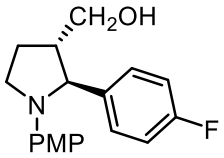
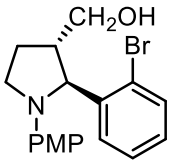
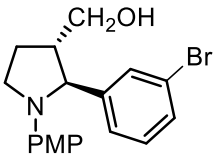
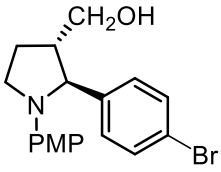
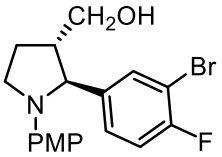
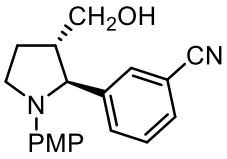
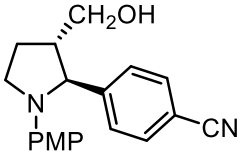
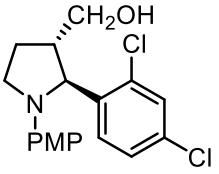
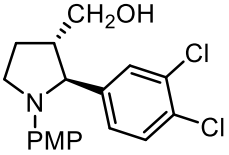
Entry	5 (xM sol.)[b]	Cat.	Conditions[a]	Yield[c] (%)	dr[d]	ee (%)[e]
1	6M	**63**	DMSO, rt, 4 h	56	20:1	89
2	6M	**66**	DMSO, rt, 5 h	48	18:1	85
3	6M	**65**	DMSO, rt, 12 h	<5	n.d.	n.d.
4	6M	**63**	DMF, rt, 6 h	50	20:1	88
5	6M	**63**	Toluene, rt, 12 h	<5	n.d.	n.d.
6	6M	**63**	CH_3CN, rt, 8 h	45	20:1	86
7	4M	**63**	DMSO, rt, 4 h	65	20:1	90
8	3M	**63**	DMSO, rt, 4 h	72	20:1	90
9	**3M**	**63**	**DMSO, 5 °C, 6 h**	**78**	**>25:1**	**96**
10	3M	**63**	DMSO, 0 °C, 8 h	69	>25:1	96
11	2M	**63**	DMSO, 5 °C, 8 h	65	>25:1	95
12[f]	3M	**63**	DMSO, 5 °C, 12 h	61	>25:1	94
13[g]	3M[g]	**63**	DMSO, 5 °C, 6 h	<10	n.d.	n.d.

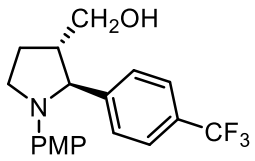
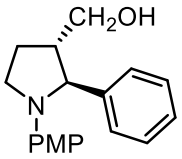
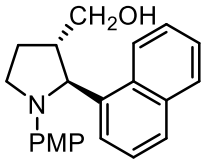
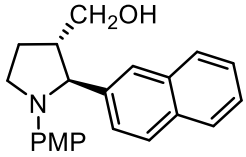
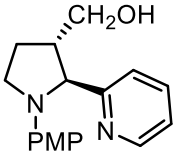
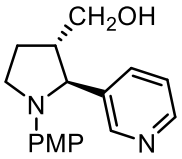
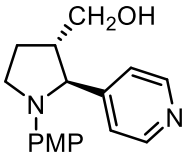
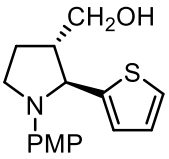
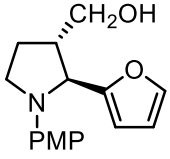
[a] (i) Imine **2** (0.3 mmol), **62** (xM sol, 0.9 mmol), catalyst **63** (20 mol %), solvent (3.0 mL) (ii) MeOH (3.0 mL). [b] see experimental data. [c] isolated yield refer to **64a** (after two steps in one pot). [d] determined by ^{1}H-NMR. [e] determined by chiral phase HPLC analysis using OD-H column and ^{i}PrOH/ Hexane solvent. [f] catalyst (10 mol%) [g] CH_3CO_2H was not added.

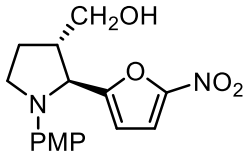
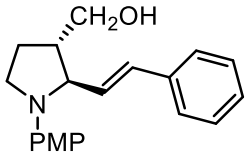
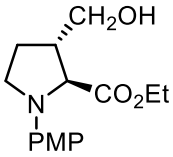
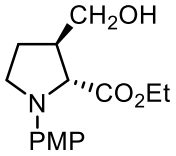
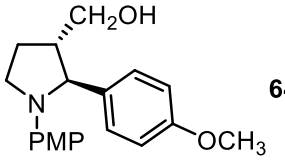
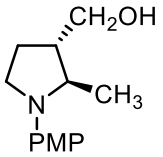
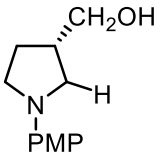
Table 2.2 Substrate scope for the synthesis of substituted pyrrolidines from various imines[a]



Entry	R	Product	64	d.r[d]	e.e[e] (%)	% Yield[c]
1	2-NO_2-C_6H_4		**64a**	>25:1	98	70
2	3-NO_2-C_6H_4		**64b**	>25:1	92	76
3	4-NO_2-C_6H_4		**64c**	>25:1	96	78
4	2-Cl-C_6H_4		**64d**	>25:1	99	61
5	3-Cl-C_6H_4		**64e**	>25:1	92	65
6	4-Cl-C_6H_4		**64f**	>25:1	90	69
7	2-F-C_6H_4		**64g**	>25:1	93	63
8	3-F-C_6H_4		**64h**	>25:1	90	67

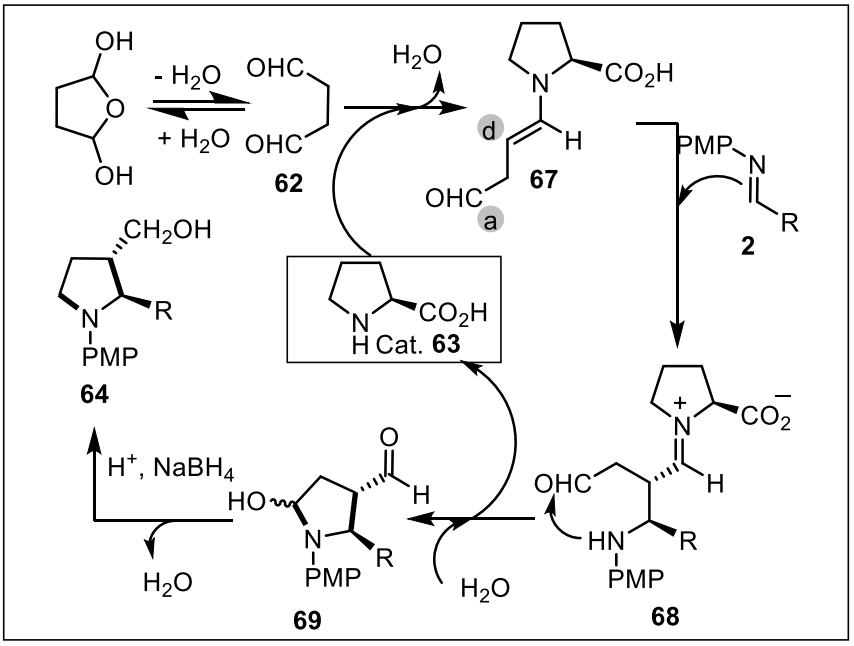
Entry	R	Product	64	d.r[d]	e.e[e] (%)	% Yield[c]
9	4-F-C_6H_4		**64i**	>25:1	91	75
10	2-Br-C_6H_4		**64j**	>25:1	96	64
11	3-Br-C_6H_4		**64k**	>25:1	93	68
12	4-Br-C_6H_4		**64l**	>25:1	90	73
13	3-Br,4-F-C_6H_4		**64m**	>25:1	92	71
14	3-CN-C_6H_4		**64n**	>25:1	93	70
15	4-CN-C_6H_4		**64o**	>25:1	95	73
16	2Cl,4-Cl-C_6H_4		**64p**	>25:1	91	61
17	3-Cl,4-Cl-C_6H_4		**64q**	>25:1	95	63

Entry	R	Product	64	d.r[d]	e.e[e] (%)	% Yield[c]
18	4-CF_3-C_6H_4		**64r**	>25:1	98	74
19	C_6H_5		**64s**	>25:1	90	62
20	1-napthyl		**64t**	>25:1	97	56
21	2-napthyl		**64u**	>25:1	90	60
22	2-pyridyl		**64v**	>25:1	95	63
23	3-pyridyl		**64w**	>25:1	88	65
24	4-pyridyl		**64x**	>25:1	98	68
25	2-thienyl		**64y**	>25:1	95	66
26	2-furyl		**64z**	>25:1	96	60

Entry	R	Product	64	d.r[d]	e.e[e] (%)	% Yield[c]
27	5-NO_2-2-furyl		**64aa**	>25:1	96	78
28	(E)-CH=CH-C_6H_5		**64ab**	>25:1	95	57
29	CO_2Et		**64ac**	>25:1	99	73
30	CO_2Et		**64ad**	>25:1	99	67
31	4-OCH_3-C_6H_4		**64ae**	n.r	n.r	n.r
32	CH_3		**64af**	n.r	n.r	n.r
33	H		**64ag**	n.r	n.r	n.r

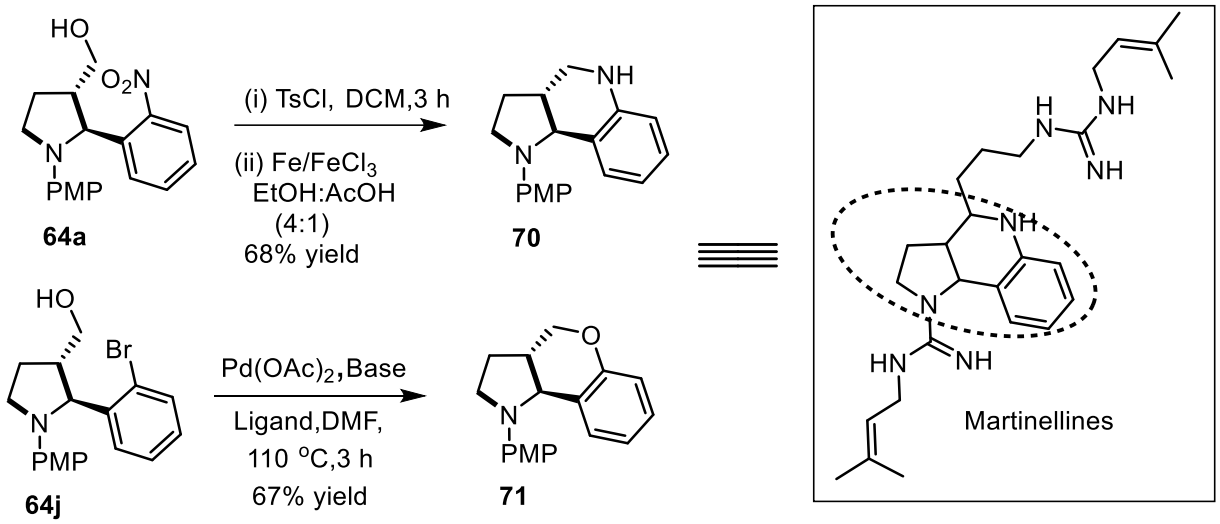
[a] (i) Imine **2** (0.3 mmol), **62** (3M sol, 0.9 mmol), **63** (20 mol %), DMSO (3.0 mL), (ii) MeOH (3.0 mL). [b]time for Mannich reaction catalyzed by **63** (20 mol %). [c]isolated yield refer to **2**. [d]determined by 1H-NMR. [e]determined by chiral phase HPLC analysis using OD-H column and *i*PrOH/Hexane as solvents.

Based on our study and literature examples on proline catalyzed Mannich reaction, the following stepwise mechanism was proposed to account for the reaction. As shown in (**Scheme 2.23**), enamine (**67**) generated from succinaldehyde (**62**) and proline (**63**), reacts with *N*-PMP aldimine (**2**) to gave *syn*-Mannich type intermediate (**68**)**.** The intermediate **(68**) undergoes cyclization to hemiaminal (**69**) with the subsequent regeneration of catalyst (**63**). The intramolecular reductive amination of (**69**) with $NaBH_4$ in the presence of acid and simultaneous aldehydic reduction affords *trans*-2, 3-disubstituted *N*-PMP pyrrolidine (**64**) in high yields and excellent diastereo (>25:1) and enantioselectivity's (up to > 99%). The formal [3+2] annulated products are versatile intermediates in organic synthesis and can be readily converted into important chiral building blocks.



Scheme 2.23 Proposed reaction mechanism for formal [3+2] cycloaddition

Having in mind the access to the martinellines and chromene skeleton, we anticipated that synthesized substituted pyrrolidine bearing an *o*-nitrophenyl and *o*-bromophenyl substituent would be a good candidate for the access to such skeletons. To further explore the synthetic application of our developed methodology, we investigated the transformation of the product (**64a**) and (**64j**) to its corresponding martenelline[111] and chromene[112-113] based core derivative (**70 and 71**) as shown in (**Scheme 2.24**).



Scheme 2.24 Synthesis of martenelline and chromene based pyrrolidines

2.5 Conclusions

In conclusion, we have developed a simple and highly stereoselective method for substituted pyrrolidines from readily available precursors like; *N*-PMP aldimines and succinaldehyde as new 1, 3-carbon dipole. The present one-pot protocol involves the L-proline catalyzed direct Mannich reaction and reductive cyclization sequence as formal [3+2] cycloaddition under a mild condition, affords a wide access to *trans*-2, 3-substituted pyrrolidines.

2.6 General Experimental Methods

All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on SiO_2 gel F254 plates. The column chromatography was performed on silica gel (100-200 meshes) using EtOAc/Hexane. All other reagents were of analytical grade and used without further purification. ^1H 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 quadrupole electrospray ionization (ESI) technique. HPLC was performed on Thermo Finnigan instrument using chiral Pack OD-H column and *i*-PrOH/Hexane solvent system.

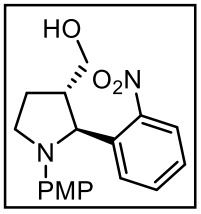
2.7 General procedure for the organocatalytic Mannich/intramolecular cyclization/ reductive amination cascade reaction

Succinaldehyde (**62**) (0.3 mL, 0.9 mmol, 3M solution) was added to a mixture of preformed *N*-PMP aldimine (**2**) (0.3 mmol) and L-proline (**63**) (7.0 mg, 0.06 mmol) in DMSO (3.0 mL) at

room temperature. The reaction mixture was stirred at 5 ^{o}C until the aldimine was consumed as monitored by TLC. The reaction was worked up by addition of saturated $NaHCO_3$ solution (3 mL) and extracted with ethyl acetate with three times. The combined organic extracts were washed with brine one time, dried over anhydrous Na_2SO_4 and concentrated in vacuum after filtration. The crude adduct was taken in MeOH (3 mL) and CH_3CO_2H (50 mol %, 9 μL) and then $NaBH_4$ was cautiously at 0 ^{o}C and further stirred for 3 h and allows it come to room temperature. The reaction was subsequently quenched with saturated $NaHCO_3$ solution (3 mL). The aqueous solution was extracted with ethyl acetate twice and combined organic extracts were washed with brine once and dried over anhydrous Na_2SO_4 and concentrated in vacuum after filtration. Purification by silica gel column chromatography (hexane: EtOAc) gave *trans*-2, 3-disubstituted pyrrolidines (**64**) with yields (56-78%).

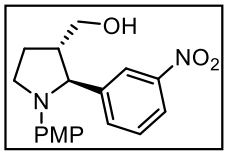
2.8 Analytical data of (64a-64ad)

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(2-nitrophenyl) pyrrolidin-3-yl) methanol (64a)



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.03-2.14 (m, 2H), 2.31-2.36 (m, 1H), 3.49-3.53 (m, 1H), 3.56-3.61 (m, 1H), 3.66-3.86 (m, 1H), 3.70 (s, 3H), 3.88-3.92 (m, 1H), 5.08 (d, *J* = 3.0 Hz, 1H), 6.37 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 1H), 7.39 (t, *J* = 7.7 Hz, 2H), 7.50 (t, *J* = 7.7 Hz, 2H), 8.02 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.59, 47.39, 50.14, 55.74, 62.21, 63.80, 112.71 (2C), 114.91 (2C), 124.84, 128.25, 129.58, 134.00, 139.60, 140.68, 147.85, 151.18; HRMS (ESI): Calcd for $C_{18}H_{20}N_2O_4$ (MH^+) 329.1501, Found 329.1497; $[\alpha]_D^{22}$ = + 18.6 (*c* 1.0, $CHCl_3$, 98% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 85:15), 1.0 mL/min; minor enantiomer t_R = 11.347 min, major enantiomer t_R = 14.273 min.

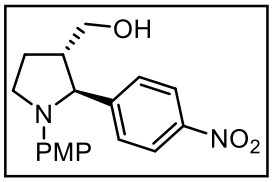
((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(3-nitrophenyl)pyrrolidin-3-yl)methanol (64b)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88-1.95 (m, 1H), 2.13-2.23 (m, 1H), 2.30-2.37 (m, 1H), 3.45 (dd, *J* = 16.3 Hz, 8.8 Hz, 1H), 3.69 (m, 2H), 3.71 (s, 3H), 3.79 (dt, *J* = 8.5 Hz, 3.2 Hz, , 1H), 4.63 (d, *J* = 2.7 Hz, 1H), 6.41 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 9.1 Hz, 2H), 7.47 (t, *J* = 8.1 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 8.08 (d, *J* = 8.0 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.49, 48.56, 51.49, 55.77, 63.84, 65.21, 113.43 (2C), 114.86(2C), 121.02, 121.95, 129.54, 132.27, 141.39, 147.11, 148.68, 151.39; HRMS (ESI): Calcd for $C_{18}H_{20}N_2O_4$ (MH^+) 329.1501, Found 329.1512; $[\alpha]_D^{22}$ = - 50.9 (*c* 1.0,

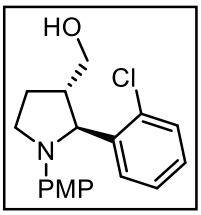
$CHCl_3$, 92% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 70:30), 1.0 mL/min; minor enantiomer t_R = 7.223 min, major enantiomer t_R = 10.713 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(4-nitrophenyl) pyrrolidin-3-yl)methanol (64c)



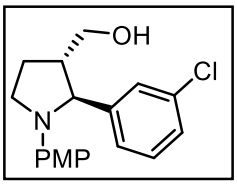
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88-1.94 (m, 1H), 2.11-2.21 (m, 1H), 2.31-2.37 (m, 1H), 3.46 (dd, *J* = 16.3 Hz, 8.8 Hz, 1H), 3.68 (m, 2H), 3.70 (s, 3H), 3.75 (dt, *J* = 8.8 Hz, 3.3 Hz, 1H), 4.63 (d, *J* = 2.8 Hz, 1H), 6.38 (d, *J* = 9.1 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.51, 48.43, 51.37, 55.75, 63.79, 65.22, 113.29 (2C), 114.84 (2C), 123.88 (2C), 126.86 (2C), 141.27, 146.84, 151.28, 152.52; HRMS (ESI): Calcd for $C_{18}H_{20}N_2O_4$ (MH^+) 329.1501, Found 329.1505; $[\alpha]_D^{22}$ = - 79.5 (*c* 1.0, $CHCl_3$, 96% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 70:30), 1.0 mL/min; minor enantiomer t_R = 8.060 min, major enantiomer t_R = 11.660 min.

((2*S*, 3*S*)- 2-(2-chlorophenyl)-1-(4-methoxyphenyl)pyrrolidin-3-yl)methanol (64d)



^{1}H NMR (300 MHz, $CDCl_3$) δ 2.01-2.12 (m, 1H), 2.37-2.39 (m, 1H), 3.51 (dd, *J* = 16.5 Hz, 9.2 Hz, 1H), 3.61-3.67 (m, 1H), 3.70 (s, 3H), 3.72-3.78 (m, 1H), 3.84-3.89 (m, 1H), 4.74 (d, *J* = 2.4 Hz, 1H), 6.35 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 7.16-7.21 (m, 3H), 7.38 (d, *J* = 6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.88, 47.72, 49.57, 55.82, 63.08, 64.20, 112.87 (2C), 114.91 (2C), 127.05, 127.55, 128.14, 129.75, 132.20, 140.75, 141.16, 151.07; HRMS (ESI): Calcd for $C_{18}H_{20}ClNO_2$ (MH^+) 318.1261, Found: 318.1259; $[\alpha]_D^{22}$ = +11.6 (*c* 1.0, $CHCl_3$, >99% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 9.726 min, major enantiomer t_R = 14.433 min.

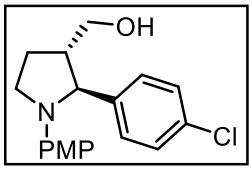
((2*S*, 3*S*)- 2-(3-chlorophenyl)-1-(4-methoxyphenyl)pyrrolidin-3-yl)methanol (64e)



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84-1.89 (m, 1H), 2.14-2.21 (m, 1H), 2.28-2.37 (m, 1H), 3.40 (dd, 16.5 Hz, *J* = 8.6 Hz, 1H), 3.60-3.65 (m, 2H), 3.70 (s, 4H), 4.47 (d, *J* = 2.1 Hz, 1H), 6.40 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 7.12-7.25 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.43, 48.32, 51.45, 55.79, 63.96, 65.29, 113.23 (2C), 114.79 (2C), 124.14, 126.03, 126.90, 129.85, 134.47, 141.65, 146.80, 151.07; HRMS (ESI): Calcd for $C_{18}H_{20}ClNO_2$ (MH^+) 318.1261, Found: 318.1265; $[\alpha]_D^{22}$

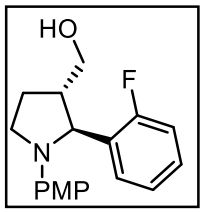
= - 33.5 (*c* 1.0, $CHCl_3$, 92% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 92:08), 1.3 mL/min; minor enantiomer t_R = 13.105 min, major enantiomer t_R = 33.857 min.

((2*S*, 3*S*)- 2-(4-chlorophenyl)-1-(4-methoxyphenyl)pyrrolidin-3-yl)methanol (64f)



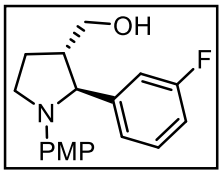
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84-1.91 (m, 1H), 2.11-2.20 (m, 1H), 2.26-2.33 (m, 1H), 3.42 (dd, *J* = 16.3 Hz, 8.8 Hz, 1H), 3.61-3.67 (m, 2H), 3.68-3.72 (m, 1H) 3.70 (s, 3H), 4.47 (d, *J* = 2.7 Hz, 1H), 6.38 (d, *J* = 9.1 Hz, 2H), 6.73 (d, *J* = 9.1 Hz, 2H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.53, 48.38, 51.58, 55.82, 64.12, 65.10, 113.28 (2C), 114.82 (2C), 127.39 (2C), 128.73 (2C), 132.30, 141.65, 142.90, 151.12; HRMS (ESI): Calcd for $C_{18}H_{20}ClNO_2$ (MH^+) 318.1261, Found: 318.1273; $[\alpha]_D^{22}$ = - 49.0 (*c* 1.0, $CHCl_3$, 90% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 92:08), 1.3 mL/min; minor enantiomer t_R = 12.338 min, major enantiomer t_R = 29.488 min.

((2*S*, 3*S*)- 2-(2-fluorophenyl)-1-(4-methoxyphenyl)pyrrolidin-3-yl)methanol (64g)



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.96-2.00 (m, 1H), 2.10-2.18 (m, 1H), 2.36-2.39 (m, 1H), 3.44-3.47 (m, 1H), 3.62-3.67 (m, 2H), 3.70 (s, 3H), 3.73-3.78 (m, 1H), 4.76 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 7.01 (t, *J* = 8.0 Hz, 1H), 7.06 (t, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.43, 47.89, 50.31, 55.82, 59.55, 64.21, 113.02 (2C), 114.86 (2C), 124.21, 126.26, 127.64, 128.27, 130.80, 133.00, 141.46, 151.10; HRMS (ESI): Calcd for $C_{18}H_{20}FNO_2$ (MH^+) 302.1556, Found 302.1548; $[\alpha]_D^{22}$ = - 11.5 (*c* 0.5, $CHCl_3$, 93% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 9.290 min, major enantiomer t_R = 18.738 min.

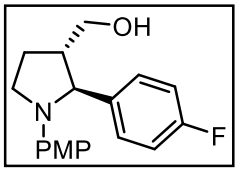
((2*S*, 3*S*)-(2-(3-fluorophenyl)-1-(4-methoxyphenyl) pyrrolidin-3-yl)methanol (64h)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85-1.95 (m, 2H), 2.17-2.24 (m, 1H), 2.33-2.38 (m, 1H), 3.45 (dd, *J* = 16.3, 8.8 Hz, 1H), 3.63-3.72 (m, 3H), 3.73 (s, 3H), 4.52 (d, *J* = 2.5 Hz, 1H), 6.45 (d, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.87-6.96 (m, 2H), 7.08 (d, J= 7.7 Hz, 1H) 7.27-7.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.50, 48.33, 51.45, 55.81, 64.10, 65.30, 112.92 113.28 (2C), 113.71, 114.78 (2C), 121.52,126.77, 130.04, 141.65, 151.08, 161.99; HRMS (ESI): Calcd for $C_{18}H_{20}FNO_2$ (MH^+)

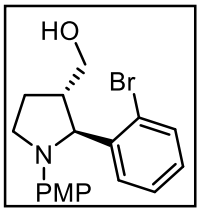
302.1556, Found 302.1561; $[\alpha]_D^{22}$ = -17.2 (*c* 1.0, $CHCl_3$, 89.5% ee); Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 21.097 min, major enantiomer t_R = 25.684 min.

((2*S*, 3*S*)- 2-(4-fluorophenyl)-1-(4-methoxyphenyl)pyrrolidin-3-yl)methanol (64i)



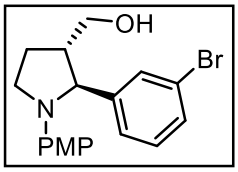
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84-1.89 (m, 1H), 2.12-2.19 (m, 1H), 2.26-2.32 (m, 1H), 3.42 (dd, *J* = 16.5 Hz, 8.8 Hz, 1H), 3.60-3.68 (m, 2H), 3.70 (s, 4H), 4.48 (d, *J* = 2.8 Hz, 1H), 6.41 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.98 (t, *J* = 8.5 Hz, 2H), 7.21 (dd, *J* = 5.5 Hz, 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.45, 48.30, 51.58, 55.78, 64.02, 64.96, 113.21 (2C), 114.77 (2C), 115.20, 115.41, 127.42, 139.87, 141.71, 150.95, 160.42, 160.85; HRMS (ESI): Calcd for $C_{18}H_{20}FNO_2$ (MH^+) 302.1556, Found 302.1562; $[\alpha]_D^{22}$ = - 37.9 (*c* 1.0, $CHCl_3$, 91% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 11.775 min, major enantiomer t_R = 28.242 min.

((2*S*, 3*S*)-(2-(2-bromophenyl)-1-(4-methoxyphenyl) pyrrolidin-3-yl) methanol (64j)



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.01–2.14 (m, 2H), 2.26–2.46 (m, 1H), 3.34–3.45 (m, 1H), 3.47-3.56 (m, 1H), 3.61–3.67 (m, 1H), 3.70 (s, 3H), 3.72 – 3.78 (m, 1H), 3.92 (dd, *J* = 10.7, 5.8 Hz, 1H), 4.68 (d, *J* = 1.4 Hz, 1H), 6.35 (d, *J* = 9.1 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 7.08–7.15 (m, 2H), 7.17– 7.22 (m, 1H), 7.58 (dd, *J* = 7.8 Hz, 7.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.75, 47.77, 49.64, 55.83, 64.22, 65.23, 112.89 (2C), 114.93 (2C), 122.34, 127.69, 127.84, 128.52, 133.05, 141.07, 142.18, 151.10; HRMS (ESI): Calcd for $C_{18}H_{20}BrNO_2$ (MH^+) 362.0755, Found 362.0761; $[\alpha]_D^{22}$ = +14.8 (*c* 1.0, $CHCl_3$, 95.66% ee); Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH = 84:16), 1.0 mL/min; minor enantiomer t_R = 13.445 min, major enantiomer t_R = 16.771 min.

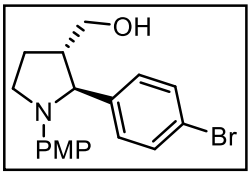
((2*S*, 3*S*)-(2-(3-bromophenyl)-1-(4-methoxyphenyl)pyrrolidin-3-yl)methanol (64k)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.90 (m, 1H), 2.17 (ddd, *J* = 15.8, 12.7, 8.3 Hz, 2H), 2.30 (qd, *J* = 7.0, 3.5 Hz, 1H), 3.36-3.43 (m, 1H), 3.59 – 3.68 (m, 2H), 3.70 (s, 3H), 4.46 (d, *J* = 2.6 Hz, 1H), 6.42 (d, *J* = 9.0 Hz, 2H), 6.76 (d, *J* = 9.0 Hz, 2H), 7.13-7.20 (m, 2H), 7.35 (dt, *J* = 6.7, 2.0 Hz, 1H), 7.42 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.40, 48.30, 51.43, 55.79, 63.96, 65.24, 113.22 (2C), 114.77 (2C), 122.80, 124.58, 128.92, 129.85, 130.17, 141.61, 147.03, 151.04; HRMS (ESI): Calcd for

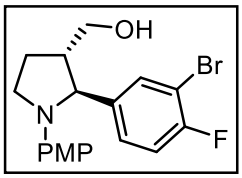
$C_{18}H_{20}BrNO_2$ (MH^+) 362.0755, Found 362.0751; $[\alpha]_D^{22}$ = -15.2 (*c* 1.0, $CHCl_3$, 92.68% ee); Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 16.570 min, major enantiomer t_R = 18.882 min.

((2*S*, 3*S*)- 2-(4-bromophenyl)-1-(4-methoxyphenyl)pyrrolidin-3-yl)methanol (64l)



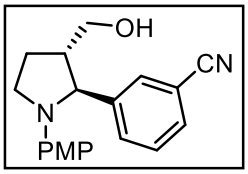
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83-1.90 (m, 1H), 2.10-2.19 (m, 1H), 2.26-2.31 (m, 1H), 3.43 (dd, *J* = 16.3 Hz, 8.6 Hz, 1H), 3.60-3.67 (m, 2H), 3.70 (s, 4H), 4.46 (d, *J* = 2.2 Hz, 1H), 6.40 (d, *J* = 9.1 Hz, 2H), 6.75 (d, *J* = 9.1 Hz, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.40 (dd, *J* = 5.5 Hz, 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.53, 48.39, 51.54, 55.83, 64.10, 65.15, 113.29 (2C), 114.84 (2C), 127.80 (2C), 128.59, 131.66 (2C), 141.63, 143.46, 151.13; HRMS (ESI): Calcd for $C_{18}H_{20}BrNO_2$ (MH^+) 362.0755, Found 362.0759; $[\alpha]_D^{22}$ = - 43.2 (*c* 1.0, $CHCl_3$, 90% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 92:08), 1.3 mL/min; minor enantiomer t_R = 12.542 min, major enantiomer t_R = 33.592 min.

((2*S*, 3*S*)-2-(3-bromo-4-fluorophenyl)-1-(4-methoxyphenyl)pyrrolidin-3-yl)methanol (64m)



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.83-1.88 (m, 1H), 2.10-2.17 (m, 1H), 2.25-2.28 (m, 1H), 3.40 (dd, *J* = 18.1 Hz, 9.5 Hz, 1H), 3.61 (d, *J* = 7.3 Hz, 2H), 3.70 (s, 4H), 4.46 (bs, 1H), 6.40 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 7.03 (t, *J* = 8.5 Hz, 1H), 7.14-7.17 (m, 1H), 7.45 (dd, *J* = 6.5 Hz, 2.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.27, 48.23, 51.37, 55.73, 63.40, 64.58, 113.21 (2C), 114.76 (2C), 126.29, 127.25, 130.68, 131.72, 141.49, 150.99, 156.45, 158.89; HRMS (ESI): Calcd for $C_{18}H_{19}BrFNO_2$ (MH^+) 380.0661, Found 380.0667; $[\alpha]_D^{22}$ = - 19.2 (*c* 1.0, $CHCl_3$, 92% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 92:08), 1.3 mL/min; minor enantiomer t_R = 12.560 min, major enantiomer t_R = 33.893 min.

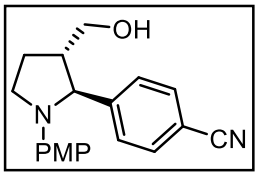
((2*S*, 3*S*)- 3-(3-(hydroxymethyl)-1-(4-methoxyphenyl) pyrrolidin-2-yl)benzonitrile (64n)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 – 1.95 (m, 1H), 2.14-2.24 (m, 1H), 2.32 – 2.38 (m, 1H), 3.46 (dd, *J* = 16.4, 8.8 Hz, 1H), 3.69 (s, 1H), 3.71 (s, 3H), 3.79 (td, *J* = 8.6, 3.0 Hz, 1H), 4.63 (d, *J* = 2.4 Hz, 1H), 6.41 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 7.47 (t, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.6 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.40, 48.41, 51.43, 55.77, 63.79, 65.02, 109.89, 113.29(2C), 114.82 (2C), 118.98, 124.12, 133.18, 134.29, 141.32, 146.18, 151.25, 158.40; HRMS (ESI): Calcd for $C_{19}H_{20}N_2O_2$ (MH^+) 309.1603, Found 309.1610; $[\alpha]_D^{22}$ = -28.4 (*c*

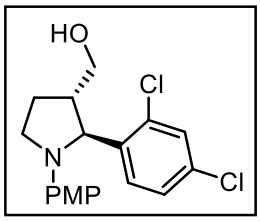
0.5, CH_2Cl_2, 93.30% ee); Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH = 90:10), 0.5 mL/min; minor enantiomer t_R = 32.745 min, major enantiomer t_R = 35.732 min.

((2*S*, 3*S*)-4-(3-(hydroxymethyl)-1-(4-methoxyphenyl) pyrrolidin-2-yl)benzonitrile (64o)



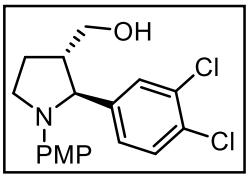
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86-1.93 (m, 1H), 2.09-2.18 (m, 1H), 2.28-2.35 (m, 2H), 3.44 (dd, *J* = 16.3, 8.9 Hz, 1H), 3.66 (d, *J* = 8.3Hz, 2H), 3.69 – 3.74 (m, 4H), 4.59 (d, *J* = 2.7 Hz, 1H), 6.37 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H) 7.58 (d, J= 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.52, 48.44, 51.42, 55.78, 63.84, 65.42, 110.51, 113.30 (2C), 114.86 (2C), 118.92, 126.85 (2C), 132.45 (2C), 141.37, 150.37, 151.32; HRMS (ESI): Calcd for $C_{19}H_{20}N_2O_2$ (MH^+) 309.1604, Found 309.1609; $[\alpha]_D^{22}$ = -36.8 (*c* 1.0, $CHCl_3$, 95.16% ee); 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 =16.330 min, major enantiomer t_R = 21.144 min.

((2*S*, 3*S*)- 2-(2, 4-dichlorophenyl)-1-(4-methoxyphenyl) pyrrolidin-3-yl)methanol (64p)



^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05-2.11 (m, 2H), 2.31-2.38 (m, 1H), 3.45 – 3.52 (m, 1H), 3.61-3.67 (m, 2H), 3.69 – 3.74 (m, 4H), 3.85 (dd, *J* = 10.7, 6.1 Hz, 1H), 4.68 (d, *J* = 1.8 Hz, 1H), 6.34 (d, *J* = 9.1 Hz, 2H), 6.76 (d, *J* = 9.1 Hz, 2H), 7.10 (s, 1H), 7.13 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.42 (d, *J* = 1.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.88, 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 $C_{18}H_{19}Cl_2NO_2$ (MH^+) 352.0871, Found 352.0877; $[\alpha]_D^{22}$ = -27.2 (*c* 0.5, CH_2Cl_2, 90.66% 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 = 36.002 min, major enantiomer t_R = 39.536 min.

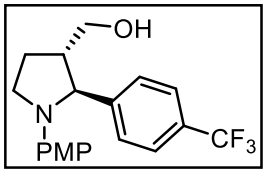
((2*S*, 3*S*)-2-(3, 4-dichlorophenyl)-1-(4-methoxyphenyl) pyrrolidin-3-yl)methanol (64q)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.92 (m, 1H), 2.10-2.19 (m, 1H), 2.28-2.37 (m, 1H), 3.38–3.45 (m, 1H), 3.66 (d, *J* = 7.2 Hz, 2H), 3.69-3.74 (m, 5H), 4.47 (d, *J* = 2.7 Hz, 1H), 6.41 (d, *J* = 9.1 Hz, 2H), 6.76 (d, *J* = 9.1 Hz, 2H), 7.10 (dd, *J* = 8.4, 1.9 Hz, 1H), 7.36 (dd, *J* = 5.2, 3.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.35, 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 $C_{18}H_{19}Cl_2NO_2$ (MH^+)

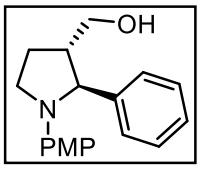
352.0871, Found 352.0877; $[\alpha]_D^{22}$ = -32.4 (*c* 0.5, CH_2Cl_2, 94.82% ee); Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH = 88:12), 0.5, mL/min; minor enantiomer t_R = 29.020 min, major enantiomer t_R = 31.550 min.

((2S, 3S)-1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)pyrrolidin-3-yl)methanol (64r)



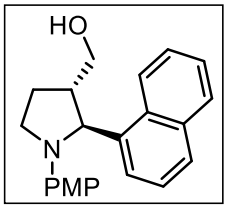
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86-1.94 (m, 1H), 2.12-2. 21 (m, 1H), 2.29 - 2.37 (m, 1H), 3.46 (dd, *J* = 16.3, 8.8 Hz, 1H), 3.65-3.69 (m, 2H), 3.71 (s, 3H), 3.72 - 3.80 (m, 2H), 4.58 (d, *J* = 2.0 Hz, 1H), 6.40 (d, *J* = 9.0 Hz, 2H), 6.75 (d, *J* = 9.0 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 2H), 7.55 (d, *J* = 8.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 25.48, 48.36, 51.43, 55.78, 64.02, 65.28, 113.23 (2C), 114.81 (2C), 125.56 (q, *J* = 3.8 Hz), 126.31(2C), 126.59, 126.84, 130.11, 141.48, 148.61, 151.13; HRMS (ESI): Calcd for $C_{19}H_{20}F_3NO_2$ (MH^+) 352.1525,Found 352.1531; $[\alpha]_D^{22}$ = - 46.4 (*c* 0.5, CH_2Cl_2, 97.54 % ee); Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH =88: 12), 0.5mL/min; major enantiomer t_R = 14.179 min, minor enantiomer t_R = 17.785 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-phenylpyrrolidin-3-yl)methanol (64s)



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.85-1.90 (m, 1H), 2.18-2.24 (m, 1H), 2.31-2.37 (m, 1H), 3.41-3.48 (dd, *J* = 17.0 Hz, 8.8 Hz, 1H), 3.62-3.73 (m, 6H), 4.49 (d, *J* = 2.8 Hz, 1H), 6.41 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 7.18-7.31 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.56, 48.34, 51.62, 55.83, 64.31, 65.65, 113.18 (2C), 114.79 (2C), 125.94 (2C), 126.70, 128.57 (2C), 141.87, 144.28, 150.89; HRMS (ESI): Calcd for $C_{18}H_{21}NO_2$ (MH^+) 284.1650, Found: 284.1660; $[\alpha]_D^{22}$ = - 41.2 (*c* 1.0, $CHCl_3$, 90% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 13.180 min, major enantiomer t_R = 29.432 min.

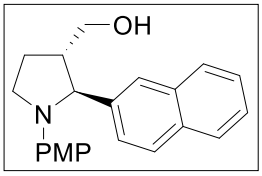
((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(naphthalen-1-yl) pyrrolidin-3-yl)methanol (64t)



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.88-1.93 (m, 1H), 2.13-2.23 (m, 1H), 2.48-2.53 (m, 1H), 3.523.59 (dd, *J* = 16.1 Hz, 9.1 Hz, 1H), 3.68 (s, 3H), 3.71-3.86 (m, 3H), 5.39 (bs, 1H), 6.38 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 6.8 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.50-7.60 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 8.6 Hz, 1H), 8.40 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.19, 47.23, 49.10, 55.85, 62.39, 64.49, 112.64 (2C), 114.93 (2C), 123.24, 123.61, 125.53,

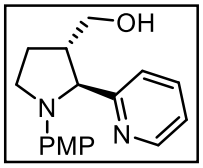
125.95, 127.40, 128.82, 128.92, 130.65, 134.16, 138.18, 141.40, 150.75; HRMS (ESI): Calcd for $C_{22}H_{23}NO_2$ (MH^+): 334.1807, Found 334.1826; $[\alpha]_D^{22}$ = +7.3 (*c* 1.0, $CHCl_3$, 97% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 15.240 min, major enantiomer t_R = 27.638 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(naphthalen-2-yl) pyrrolidin-3-yl)methanol (64u)



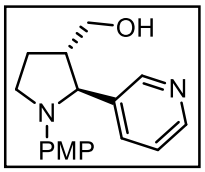
^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89-1.94 (m, 1H), 2.21-2.26 (m, 1H), 2.40-2.44 (m, 1H), 3.46 (dd, *J* = 16.5 Hz, 8.5 Hz, 1H), 3.68 (bs, 4H), 3.71-3.77 (m, 2H), 4.64 (d, *J* = 2.2 Hz, 1H), 6.47 (d, *J* = 8.8 Hz, 2H), 6.71 (d, *J* = 8.8 Hz, 2H), 7.40-7.46 (m, 3H), 7.75-3.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.63, 48.51, 51.49, 55.82, 64.28, 65.96, 113.31 (2C), 114.81 (2C), 124.38, 124.49, 125.44, 126.00, 127.64, 127.78, 128.31, 128.49, 132.67, 133.48, 141.99, 150.98; HRMS (ESI): Calcd for $C_{22}H_{23}NO_2$ (MH^+): 334.1807, Found 334.1815; $[\alpha]_D^{22}$ = - 19.6 (*c* 0.5, $CHCl_3$, 90% ee);
Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R = 18.290 min, major enantiomer t_R = 37.092 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(pyridin-2-yl) pyrrolidin-3-yl)methanol (64v)



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.77-1.85 (m, 1H), 2.06-2.14 (m, 1H), 2.47-2.54 (m, 1H), 3.56 (dd, *J* = 16.3 Hz, 8.4 Hz, 1H), 3.71 (bs, 4H), 3.78-3.80 (m, 2H), 4.64 (d, *J* = 5.5 Hz, 1H), 6.40 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.57-3.81 (dt, *J* = 7.8 Hz, 1.4 Hz, 1H), 8.55 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.49, 48.95, 49.80, 55.73, 64.91, 68.01, 113.46 (2C), 114.75 (2C), 120.24, 121.89, 137.31, 141.66, 148.83, 151.14, 163.33; HRMS (ESI): Calcd for $C_{17}H_{20}N_2O_2$ (MH^+) 285.1603, Found: 285.1635; $[\alpha]_D^{22}$ = - 37.7 (*c* 1.0, $CHCl_3$, 95% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 80:20), 1.0 mL/min; major enantiomer t_R = 10.297 min, minor enantiomer t_R = 14.238 min.

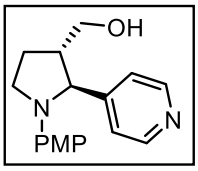
((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(pyridin-3-yl) pyrrolidin-3-yl) methanol (64w)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89-1.95 (m, 1H), 2.14-2.23 (m, 1H), 2.32-2.37 (m, 1H), 3.45 (dd, *J* = 16.3, 8.8 Hz, 1H), 3.62-3.68 (m, 2H), 3.70 (s, 3H), 3.72-3.78 (m, 2H), 4.59 (d, *J* = 2.8 Hz, 1H), 6.41 (d, *J* = 9.0 Hz, 2H), 6.75 (d,

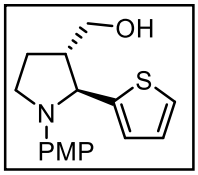
J = 9.0 Hz, 2H), 7.22 (dd, *J* = 6.6, 4.9 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 8.53 (d, *J* = 33.0 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.52, 48.43, 51.59, 55.76, 62.07, 63.26, 113.33 (2C), 114.80 (2C), 123.62, 134.06, 135.02, 141.46, 147.63, 148.89, 151.14; HRMS (ESI): Calcd for $C_{17}H_{20}N_2O_2$ (MH^+) 285.1603, Found: 285.1608; $[\alpha]_D^{22}$ = -31.8 (*c* 1.0, $CHCl_3$, 88.22% ee); 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 = 20.585 min, major enantiomer t_R = 23.286 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(pyridin-4-yl) pyrrolidin-3-yl) methanol (64x)



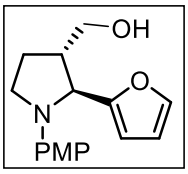
^{1}H NMR (300 MHz, $CDCl_3$) δ 2.26-2.34 (m, 1H), 2.37-2.43 (m, 1H), 2.96-2.98 (m, 1H), 3.33 (dd, *J* = 16.1 Hz, 9.6 Hz 1H), 3.71 (s, 4H), 3.74-3.82 (m, 2H), 5.02 (d, *J* = 2.2 Hz, 1H), 6.40 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 7.21 (d, *J* = 5.9 Hz, 2H), 8.53 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.88, 29.64, 48.15, 55.71, 59.88, 61.60, 113.58 (2C), 114.87 (2C), 121.28 (2C), 140.65, 149.99 (2C), 151.83, 152.70; HRMS (ESI): Calcd for $C_{17}H_{20}N_2O_2$ (MH^+) 285.1603, Found: 285.1608; $[\alpha]_D^{22}$ = +7.2 (*c* 1.0, $CHCl_3$, 98% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 80:20), 1.0 mL/min; minor enantiomer t_R = 12.457 min, major enantiomer t_R = 16.562 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(thiophen-2-yl) pyrrolidin-3-yl)methanol (64y)



^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87-1.94 (m, 1H), 2.25-2.34 (m, 1H), 2.42-2.48 (m, 1H), 3.36 (dd, *J* = 16.5 Hz, 8.3 Hz 1H), 3.62-3.68 (m, 3H), 3.71 (s, 3H), 4.76 (d, *J* = 2.2 Hz, 1H), 6.53 (d, *J* = 8.8 Hz, 2H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.91-6.93 (m, 2H), 7.12 (dd, *J* = 1.7 Hz, 4.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.32, 33.76, 45.13, 56.78, 59.46, 62.76, 113.58, 114.87, 124.54, 124.88, 130.24, 135.04, 142.08, 151.76; HRMS (ESI): Calcd for $C_{16}H_{19}NO_2S$ (MH^+) 290.1212, Found 390.1225; $[\alpha]_D^{22}$ = - 15.8 (*c* 1.0, $CHCl_3$, 95% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 92:08), 1.3 mL/min; minor enantiomer t_R = 14.488 min, major enantiomer t_R = 32.368 min.

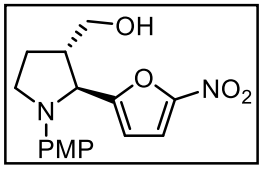
((2*S*, 3*S*)-2-(furan-2-yl)-1-(4-methoxyphenyl) pyrrolidin-3-yl)methanol (64z)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87-1.94 (m, 2H), 2.22-2.31 (m, 1H), 2.53-2.60 (m, 1H), 3.37 (dd, *J* = 16.2 Hz, 16.4 Hz 1H), 3.53-3.59 (m, 1H), 3.65 (dd, J= 7.6 Hz, 6.6 Hz, 2H), 3.73 (s, 3H), 4.61 (d , J= 2.2 Hz, 1H), 6.06 (d, *J* = 3.1 Hz, 1H), 6.26 (dd, *J* = 3.0 Hz, 2.9 Hz, 1H), 6.54 (d, J= 9.0 Hz, 2H),6.79 (d, *J* = 9.0 Hz, 2H), 7.33 (s,

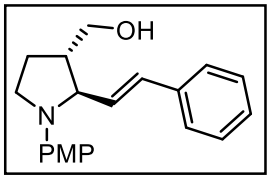
1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.87, 47.54, 47.89, 55.82, 59.61, 64.28, 105.98, 110.14, 113.35(2C),114.76 (2C), 141.45, 141.78, 151.27, 156.07; HRMS (ESI): Calcd for $C_{16}H_{19}NO_3$ (MH^+) 274.1444, Found 274.1450; $[\alpha]_D^{22}$ = - 39.6 (*c* 1.0, $CHCl_3$, 95.90% ee); Enantiomeric excess was determined by HPLC with a Chiralpak IA column (*n*-Hexane: *i*-PrOH = 90:10), 1.0 mL/min; minor enantiomer t_R =20.544 min, major enantiomer t_R = 23.942 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(5-nitrofuran-2-yl) pyrrolidin-3-yl)methanol (64aa)



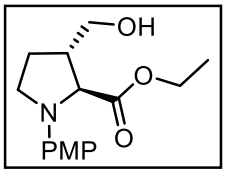
^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94-2.00 (m, 1H), 2.16-2.23 (m, 1H), 2.60-2.66 (m, 1H), 3.38 (dd, *J* = 16.1 Hz, 8.5 Hz, 1H), 3.56-3.68 (m, 3H), 3.72 (s, 3H), 4.70 (bs, 1H), 6.29 (d, *J* = 3.8 Hz, 1H), 6.48 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 2H), 7.19 (d, *J* = 3.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.74, 47.52, 48.04, 55.77, 59.49, 63.62, 109.90, 112.79, 113.36 (2C), 114.92 (2C), 140.91, 151.61, 151.81, 160.91; HRMS (ESI): Calcd for $C_{16}H_{18}N_2O_4$ (MH^+) 319.1294, Found 334.1296; $[\alpha]_D^{22}$ = - 58.8 (*c* 0.5, $CHCl_3$, 96% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 85:15), 1.3 mL/min; minor enantiomer t_R = 19.330 min, major enantiomer t_R = 26.727 min.

((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-((*E*)-styryl) pyrrolidin-3-yl)methanol (64ab)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-1.90 (m, 1H), 2.18-2.24 (m, 1H), 2.32-2.36 (m, 1H), 3.34 (dd, *J* = 16.5 Hz, 8.3 Hz, 1H), 3.52-3.68 (m, 3H), 3.73 (s, 3H), 4.10 (bs, 1H), 6.20 (dd, *J* = 15.9 Hz, 5.8 Hz, 1H), 6.48 (d, *J* = 15.9 Hz, 1H), 6.59 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 7.26-7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.65, 48.10, 55.75, 60.32, 63.42, 63.77, 113.17 (2C), 114.67 (2C), 126.22 (2C), 127.16, 128.37 (2C), 129.69, 131.61, 136.77, 142.20, 150.81; HRMS (ESI): Calcd for $C_{20}H_{23}NO_2$ (MH^+) 310.1807, Found 310.1819; $[\alpha]_D^{22}$ = -54.3 (*c* 1.0, $CHCl_3$, 95% ee); Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (*n*-Hexane: *i*-PrOH = 90:10), 1.3 mL/min; minor enantiomer t_R = 13.307 min, major enantiomer t_R = 27.058 min.

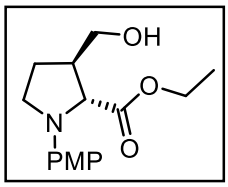
Ethyl (2*S*, 3*S*)-3-(hydroxymethyl)-1-(4-methoxyphenyl)pyrrolidine-2-carboxylate (64ac)



^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.1 Hz, 3H), 1.81-1.94 (m, 1H), 2.25 (dt, *J* = 15.0, 7.7 Hz, 1H), 2.52-2.63 (m, 1H), 3.40 (dd, *J* = 15.4 Hz, 7.7 Hz 1H), 3.52 (td, *J* = 8.5, 4.8 Hz, 1H), 3.64 (d, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 3.75-3.85 (m, 1H), 4.11 (d, *J* = 3.1 Hz, 1H),4.12 – 4.21 (m, 2H), 6.49 (d, *J* = 9.0 Hz, 2H), 6.81

(d, *J* = 9.0Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.18, 26.25, 46.41, 47.64, 55.76, 60.96, 63.74, 64.52, 112.90 (2C),114.85 (2C), 141.28, 151.42, 174.41; HRMS (ESI): Calcd for $C_{15}H_{21}NO_4$ (MH^+) 280.1550, Found 280.1556; $[\alpha]_D^{22}$= - 43.8 (*c* 0.5, $CHCl_3$, 99.34 % ee); Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH =92: 08), 0.5mL/min; minor enantiomer t_R = 26.319 min, major enantiomer t_R = 28.674 min.

Ethyl (2*R*, 3*R*)-3-(hydroxymethyl)-1-(4-methoxyphenyl)pyrrolidine-2-carboxylate (64ad)

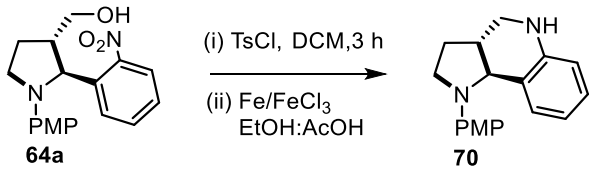


^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, *J* = 7.2 Hz,7.0 Hz, 3H), 1.83-1.91 (m, 1H), 2.20-2.29 (m, 2H), 2.54-2.61 (m, 1H), 3.40 (dd, *J* = 15.2 Hz, 15.6 Hz 1H), 3.50-3.55 (m, 1H), 3.64 (d, *J* = 7.2 Hz, 2H), 3.73 (s, 3H), 4.11-4.20 (m, 3H), 6.49 (d, *J* = 9.0 Hz, 2H), 6.81 (d, *J* = 9.0Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.18, 26.25, 46.41, 47.64, 55.76, 60.96, 63.74, 64.52, 112.90 (2C),114.85 (2C), 141.28, 151.42, 174.41; HRMS (ESI): Calcd for $C_{15}H_{21}NO_4$ (MH^+) 280.1550, Found 280.1556; $[\alpha]_D^{22}$ = + 26.6 (*c* 0.5, $CHCl_3$, 99.34 % ee); Enantiomeric excess was determined by HPLC with a Chiralpak IB column (*n*-Hexane: *i*-PrOH =92: 08), 0.5mL/min; minor enantiomer t_R = 28.487 min, major enantiomer t_R = 26.365 min.

2.9 General procedure for the synthesis of (3aR, 9bS)-1-(4-methoxyphenyl)-2, 3,3a, 4, 5, 9*b*-hexahydro-1*H*-pyrrolo-[3, 2-*c*] quinoline (70)

To a stirred solution of compound (**64a**) (100 mg, 0.3 mmol) in CH_2Cl_2 (3 mL) was added Et_3N (3.0 equiv, 0.9 mmol) at rt. Reaction was taken to 0 ^oC and TsCl (68 mg, 0.36 mmol) in CH_2Cl_2 was added drop wise 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 concentrated under vacuo to give crude solid mass. This was used further for next step without purification at this stage. To this crude mass was added ethanol and acetic acid (5mL, 4:1 ratio respectively) and Iron powder (125 mg, 7.5 equiv, 2.2 mmol) was added while stirring followed by $FeCl_3$ (9.5 mg, 0.2 equiv, 0.06 mmol). The reaction mixture was refluxed for 6 hours which was monitored by TLC. After completion of the reaction, ethanol was evaporated through rotavapour. Dichloromethane (10 ml) was added and stirred. The reaction mixture was filtered through celite and washed with the dichloromethane (10 ml). The organic layer was quenched with saturated $NaHCO_3$ solution (10 ml) and extracted 3 times with dichloromethane (10x3). The organic layer was dried over sodium sulphate and the crude residue so obtained was purified by

column chromatography (EtOAc/hexanes) to afford (**70**) as brownish pasty liquid (54mg, 68% yield) as shown in (**Scheme 2.25**).

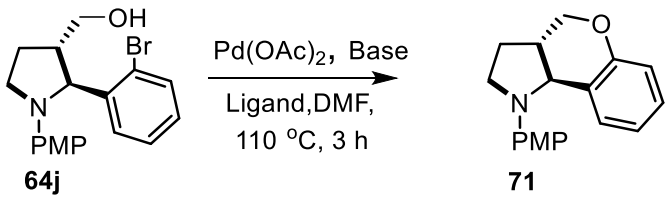


Scheme 2.25 Synthesis of martenelline based pyrrolidines

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, *J* = 7.7 Hz, 1H), 7.00 (ddd, *J* = 8.1, 7.4, 0.9 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 2H), 6.75 (d, *J* = 9.1 Hz, 2H), 6.61 (td, *J* = 7.6, 1.1 Hz, 1H), 6.52 (dd, *J* = 8.0, 1.0 Hz, 1H), 4.81 (d, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.62 (dd, *J* = 11.7, 4.3 Hz, 1H), 3.46-3.51 (d, *J* = 8.4 Hz, 1H), 3.18-3.26 (m, 2H), 2.54-2.63 (m, 1H), 2.11-2.22 (m, 1H), 2.01– 2.07 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.66, 145.65, 144.82, 128.09, 127.62 (2C), 120.14, 117.02, 115.98, 114.83(2C), 113.63, 56.73, 55.77, 46.57, 42.16, 31.50, 24.30; HRMS (ESI): Calcd for $C_{18}H_{19}N_2O$ (MH^+) 281.1654,Found 281.1661; $[\alpha]_D^{25}$ = + 23.6 (*c* 0.5, CH_2Cl_2,).

2.10 General procedure for the synthesis of (3aS, 9bS)-1-(4-methoxyphenyl)-1,2,3,3a,4,9*b*-hexahydrochromeno [4,3-*b*]pyrrole (**71**)

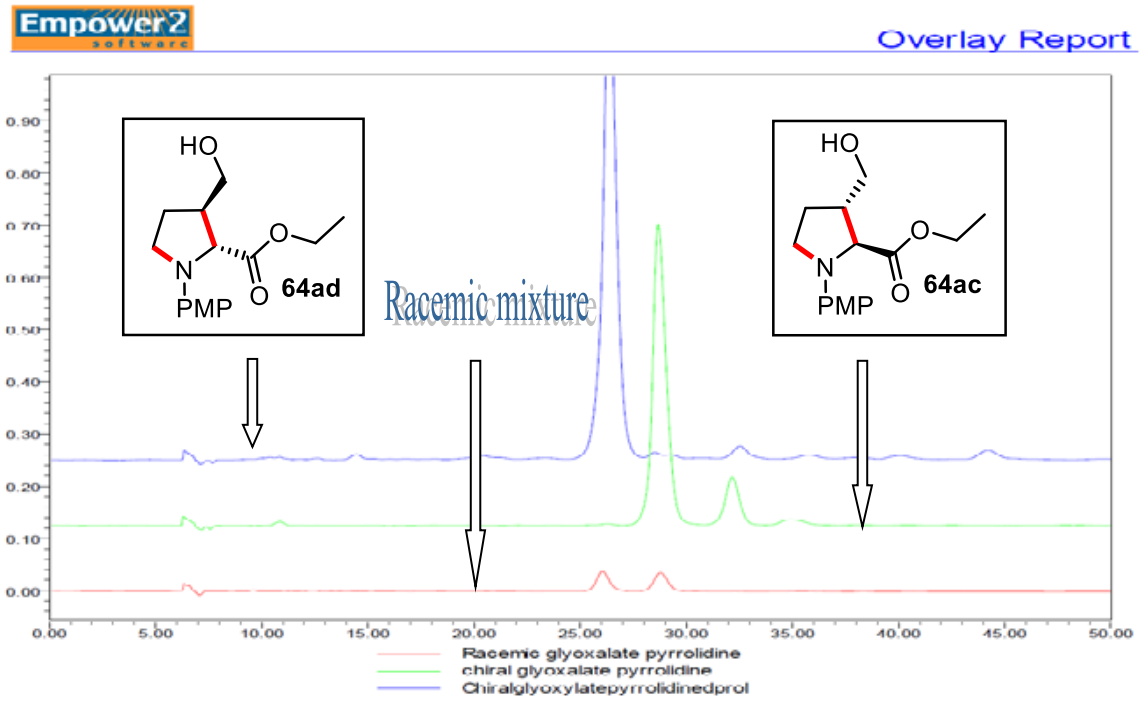
In a two-necked round bottomed flask fitted with condenser, substrate (**64j**) (0.05g, 0.15 mmol), KO^{t}Bu (33 mg, 0.3 mmol), and Pd $(OAc)_2$ (1.2 mg, 2 mol %), PPh_3 (7.8 mg, 20 mol %), in DMF (3 mL) at refluxing condition under nitrogen atmosphere were placed and the reaction mixture was allowed to react at 110^{o}C for 3 h. It was allowed to cool to rt and extracted with EtOAc (3 x10 mL). Then the organic part was washed with water and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave crude product which was then purified through column chromatography by using silica gel (100–200 mesh) and pet ether/EtOAc (90:10) as eluent. The product (**71**) was obtained as colorless oil in (29 mg, 67%) as shown in (**Scheme 2.26**).

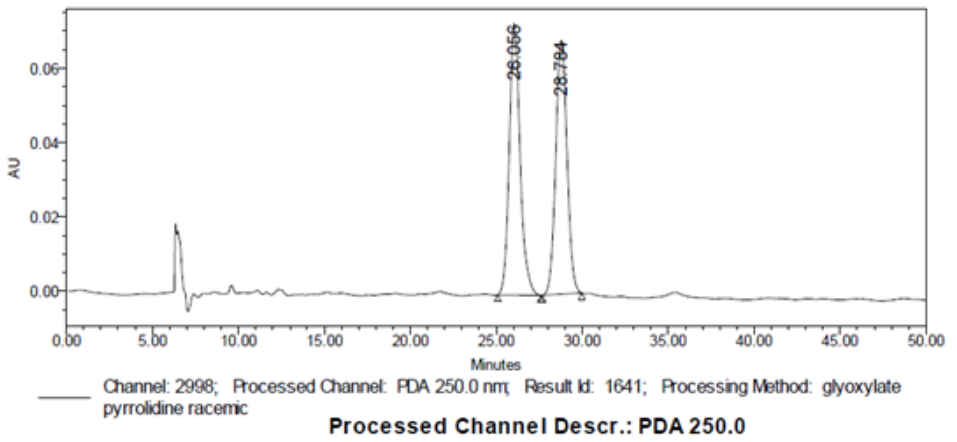


Scheme 2.26 Synthesis of chromene based pyrrolidines

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (dt, *J* = 7.4, 1.2 Hz, 1H), 7.18 (dd, *J* = 8.7, 4.1 Hz, 1H), 7.14 - 7.17 (m, 2H), 6.76 (d, *J* = 9.1 Hz, 2H), 6.36 (d, *J* = 9.1 Hz, 2H), 4.74 (d, *J* = 1.8 Hz, 1H), 3.85 (dd, *J* = 15.9, 10.0 Hz, 1H), 3.72 - 3.77 (m, 1H), 3.70 (s, 3H), 3.66 (dt, *J* = 18.8, 5.8 Hz, 1H), 3.47-3.53 (m, 1H), 2.35-2.41 (m, 1H), 2.02 - 2.15 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.26, 147.89, 140.67, 139.67, 133.65, 128.51, 127.92, 125.31, 114.94 (2C), 112.76 (2C), 62.24, 55.78, 50.21, 47.44, 29.67, 24.67; HRMS (ESI): Calcd for $C_{18}H_{19}NO_2$ (MH^+) 282.1494, Found 282.1500; $[\alpha]_D^{25}$ = + 19.6 (*c* 0.5, CH_2Cl_2,).

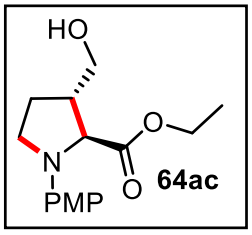
Further HPLC data analysis of **64ac and 64ad** is shown below in (**Figure 2.4)** with overlay comparison of both the enantiomers which were prepared using L- proline and D- proline separately as an organocatalyst for the generation of differently substituted enantiomers of proline derivatives by using our own developed methodology. A ^{1}H and ^{13}C NMR spectra of compound (**64c**) is shown in (**Figure 2.5).**

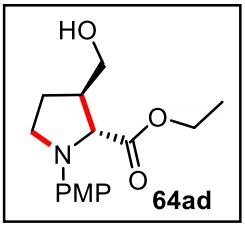




Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	26.056	3206487	50.70	72971
2	PDA 250.0 nm	28.784	3117652	49.30	68318





Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	26.365	82907543	99.67	1821516
2	PDA 250.0 nm	28.487	278594	0.33	10914

Processed Channel Descr.: PDA 250.0 nm

	Processed Channel Descr.	RT	Area	% Area	Height
1	PDA 250.0 nm	26.319	169494	0.33	4945
2	PDA 250.0 nm	28.674	51182430	99.67	1132964

Figure 2.4 HPLC report of two different enatiomers of pyrrolidine derivatives (**64ac** and **64ad**)

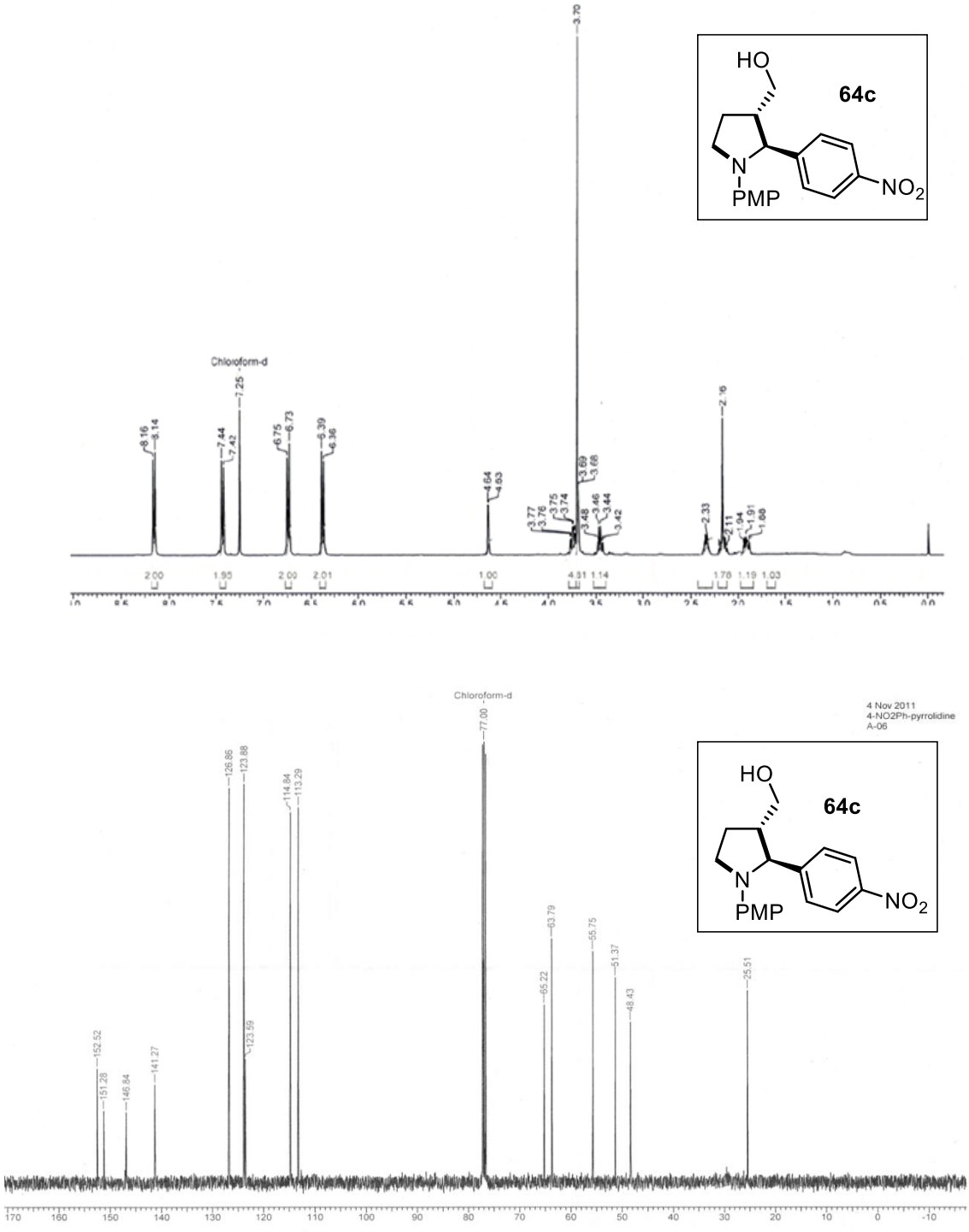


Figure 2.5 ^{1}H and ^{13}C NMR spectra of (2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(4-nitrophenyl) pyrrolidin-3-yl)methanol (**64c**)

2.11 Crystal structure of ((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(3-nitrophenyl) pyrrolidin-3-yl) methanol (64b)

The Single Crystal X-ray data for ((2*S*, 3*S*)-1-(4-methoxyphenyl)-2-(3-nitrophenyl) pyrrolidin-3-yl) methanol (**64b**) are summarized in (**Table 2.3)**. The CIF for this structure has been deposited at Cambridge Crystal Data Centre (**CCDC No: 864411**).Crystal data and other experimental details are given in (**Table 2.3)**. Bond distances and angles in ((2S, 3S)-1-(4-methoxyphenyl)-2-(3-nitrophenyl)pyrrolidin-3-yl)methanolare in agreement with the theoretical values (Allen, et al., 1987).The pyrrolidine ring is in envelope conformation and makes a dihedral angle of 11.42(8)^{o} with the phenyl ring (C6-C11). Phenyl ring (C15-C20) is almost perpendicular to the pyrrolidine ring (dihedral angle 88.78(8)^{o}). Pyrrolidine has *envelope* conformation with the best mirror plane passing through C3 bisecting the opposing bond (N1-C5). The asymmetry parameter is**:** ΔC_s (C3) = 5.6. Our X-ray analysis of substituted pyrrolidine **(64b**) has further established the relative stereochemistry. The ORTP-model shown in (**Figure 2.6**) has C2-*S* and C3-*S* stereochemistry, as expected through the L-proline (**63**) catalyzed *syn*-selective direct Mannich reaction, followed by reductive cyclization. Displacement ellipsoids are drawn at the 40% probability level and H atoms are shown as small spheres of arbitrary radii

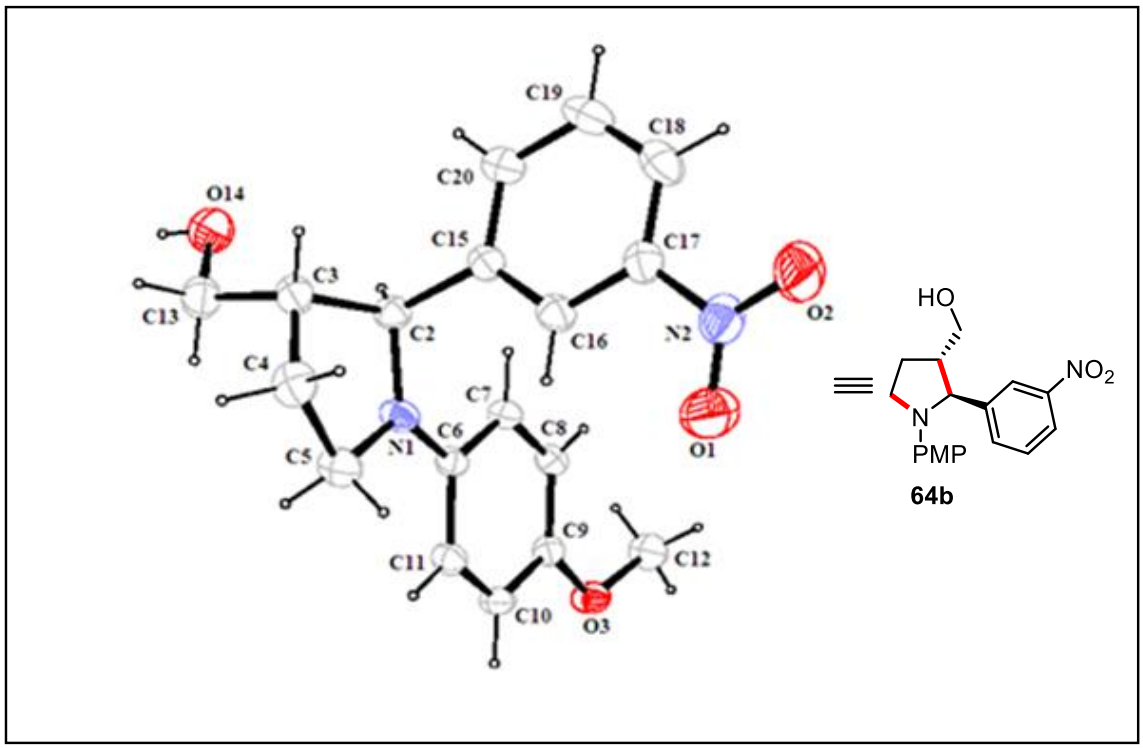


Figure 2.6 Single-crystal X-ray analysis of **64b**

Table 2.3 Crystal data for **64b**

CCDC	**864411**
Crystal description	Red coloured block shaped
Crystal size	0.30 x 0.20 x 0.10 mm
Empirical formula	C_{18} H_{20} N_2 O_4
Formula weight	328.36
Measurement	*X'calibur system–Oxford diffraction make , U.K.*
Radiation, Wavelength	MoKα, 0.71073 Å
Cell measurement Temperature	293(2) K
Unit cell dimensions	a= 7.2761(4), b= 7.6312(5)
	c = 14.6614(10) Å; β= 95.224(5)º
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell volume	810.70(9) $Å^3$
Density (calculated)	1.345Mgm^{-3}
No. of molecules per unit cell, Z	2
Absorption coefficient	0.096 mm^{-1}
F(000)	348
Refinement of unit cell	4103 reflections for 3.7698<θ< 29.0804 º
Scan mode	w scans
θ range for entire data collection	3.78 <θ< 26.00 º
Range of indices	*h* = -8 to 8, *k* =-9 to 9, *l* = -18 to 18
Reflections collected / unique	15385 / 3157
Reflections observed (I > 2σ(I))	2266
R_{int}	0.0568
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	218
Final R- factor	0.0467
wR(F^2)	0.0920
Goodness-of-fit	1.041
Final residual electron density	-0.145 < Δρ < 0.189 $eÅ^{-3}$

2.12 References

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Chapter III

PART-I: Proline catalyzed two-pot synthesis of substituted pyrrole-3-carboxaldehydes

3.1 Introduction

Pyrrole is one of the most relevant nitrogen heterocyclic ring system which is found in a broad range of natural products and drug molecules. The ready availability of suitably substituted and functionalized pyrrole derivatives is essential for the progress of many branches of science including biology, pharmacology, material sciences, agrochemicals, dyes, photographic chemicals, perfumes and other organic compounds. Pyrrole was first detected by F. F. Runge[1] in 1834, as a constituent of coal tar. In 1857, it was isolated from the pyrolysate of bone. Its name comes from the Greek pyrros ("fiery") from the reaction used to detect it the red color that it imparts to wood when moistened with hydrochloric acid.[2]

3.2 Chemical reactivity

Pyrrole is a colorless volatile liquid that darkens readily upon exposure to air and is usually purified by distillation immediately before use.[3] Pyrrole is weakly basic, with a conjugate acid having pK_a of -3.8. The most thermodynamically stable pyrrolium cation is formed by protonation at the *α*-position. Pyrrole is also weakly acidic at the N-H position, with a pK_a of 17.5. Due to its aromatic character, its reactivity is similar to that of benzene and aniline (**Figure 3.1**).

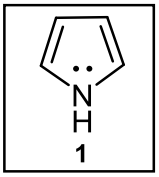
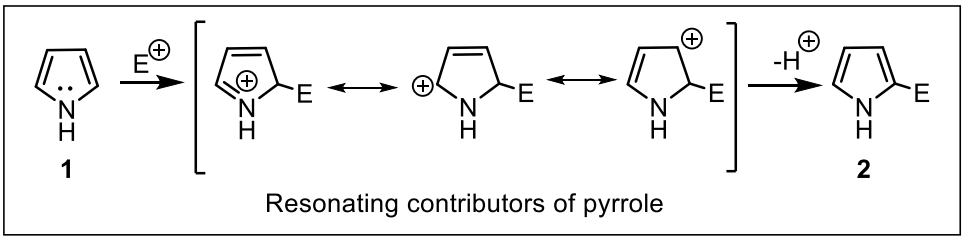


Figure 3.1 Structure of pyrrole

Pyrroles generally react with electrophiles at *α*-position (C2 or C5), due to the highest degree of stability of the protonated intermediate. As is typical for electrophilic additions to pyrroles, generally occurs at α-position as shown in (**Scheme 3.1**).



Scheme 3.1 Intermediate for *α*-attack by electrophile

3.3 Importance of pyrrole

Pyrroles are one of the most frequently appearing five-membered rings in many important molecules being useful building blocks in organic synthesis and makes them efficient starting materials for many kinds of synthetic transformations.[4-8] Pyrrole nucleus is widespread in nature and is the key structural fragment of many important bioactive molecules such as pentabromopseudodiline and pioluteorine, both isolated from bacterial sources prominent in marine natural products.[9] Ningalins and Lamellarins a wide variety of anticancer drugs, antibiotics and protease inhibitors,[10-12] showing multidrug resistance reversal activity against L1210 and HCT116 cell lines.[13-17] Nakamuric acid, axially chiral marinopyrroles which showed good activity against metacillin-resistant staphylococcus aureus strains, the bacterial red pigment.[18-19] Prodigiosin which are synthesized by bacteria belonging to the Serratia genus, having antibiotic properties.[20] Lamellarins K and L possess biological activities which include cytotoxicity, HIV-1 integrase inhibition, and multidrugresistance reversal.[21-23] Storniamide family, isolated from a variety of marine organisms (mollusks, ascidians, sponges) and containing 3,4-diarylpyrrole fragments showing potent activity as inhibitors of the multidrug resistance (MDR) phenomenon,[24] which can be considered as the main obstacle to successful anticancer chemotherapy.

Besides the classical example of the tetrapyrrole nucleus of the porphyrins and hemoglobin, pyrrole substructures are present in a large number of bioactive compounds and have been proven to display a variety of physiological activities[25-26] including HIV fusion inhibitors,[27] anti-tubercular,[28-29] antibacterial,[30] antiviral,[31] anti-inflammatory[32] and to inhibit cytokine-mediated diseases.[33] Additionally, they have been found to show potent inhibiting platelet aggregation[34] and hypertensive activities.[35] A good example for this case is atorvastatin calcium, the active material of famous drug named as “Atorvastatin” (produced by Pfizer drug company). This drug has the blood cholesterol lowering activity and one of the top-selling drugs worldwide as shown in (**Figure 3.2**).

Recently, tetra-arylpyrroles were discovered to have remarkable potential application in materials chemistry showing the existence of semiconducting materials derived from hexa (N-pirrolyl) benzene,[36] glucose sensors based on polypyrrole-latex materials[37] and polypyrrole materials for the detection and discrimination of volatile organic compounds.[38] Derivatives of the 4, 4-difluoro-4-boradipyrrin system (BODIPY) have a strong absorption in the UV and emit

very intense fluorescence. These compounds have many applications as chemosensors, for laser manufacture, image diagnosis, etc.[39] Some representative examples of pyrrole-containing secondary metabolites are summarized in (**Figure 3.2**).

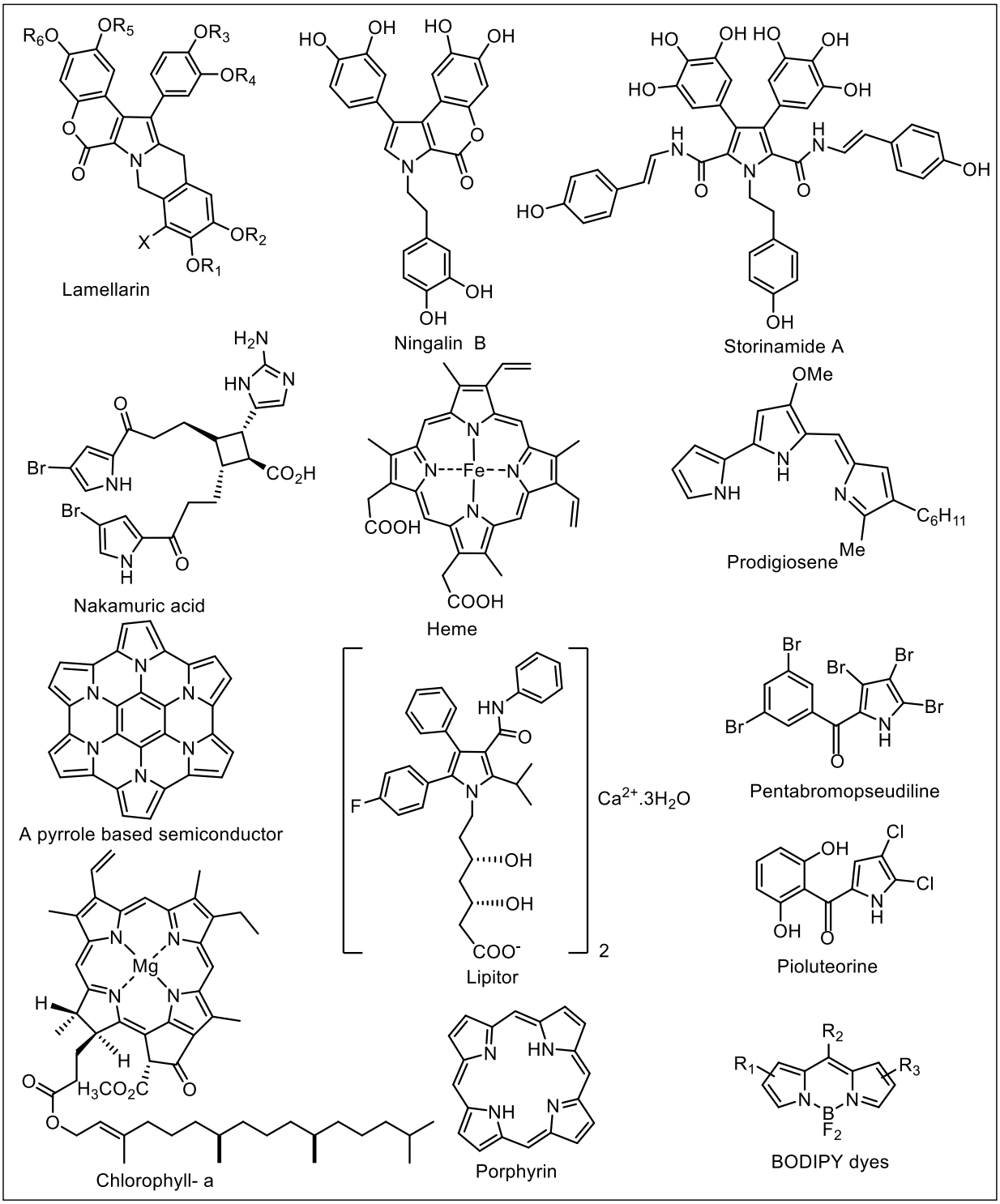
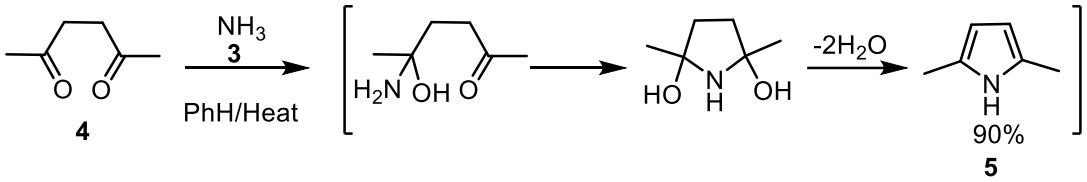


Figure 3.2 Some pyrrole-containing bioactive natural products

3.4 General Synthesis of Pyrrole Derivatives

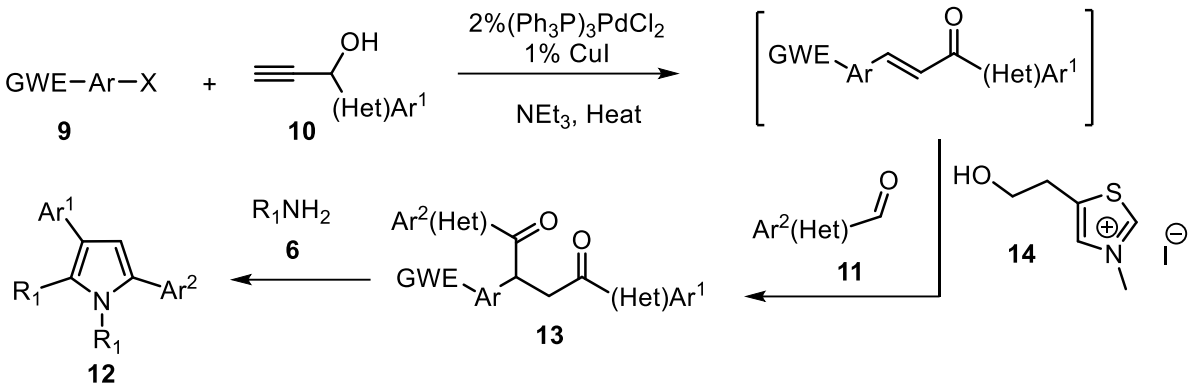
Apart from the commercial synthesis of pyrroles, there are three important approaches to pyrroles from non-heterocyclic precursors. These approaches are Paal-Knorr, Hantzsch and Knorr synthesis. In addition to these famous methods, transition metal mediated cycloisomerization-type or cycloadition-type reactions have become popular recently.[40]

The Paal-Knorr condensation is one of the classical methods for the synthesis of pyrroles, where 1, 4-dicarbonyl unit provides four carbon atoms of the ring and an amine group provides the nitrogen atom of the pyrrole (**Scheme 3.2**).[41-42] Nucleophilic addition of the amine (**3**) to the two carbonyl carbon atoms and the loss of the two moles of water afford the pyrrole. This method provides a convenient method for the synthesis of pyrroles having alkyl or aryl substituents in both 2- and 5-positions. In particular, a wide variety of 1-substituted 2, 5-dimethyl pyrroles (**5**) has been prepared from hexane-2,5-dione (**4**).



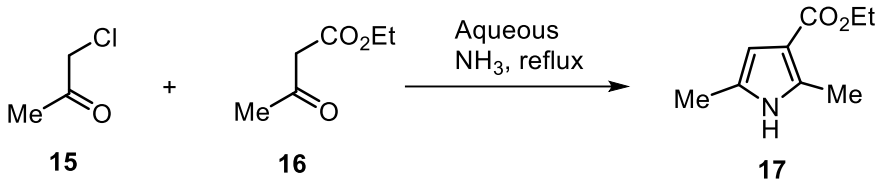
Scheme 3.2 Synthesis of pyrroles from hexane-2, 5-dione, and amine

In literature, there are many studies in which Paal-Knorr synthesis is chosen as the model method for pyrrole synthesis. They differ only in the way that the 1,4-dicarbonyl skeleton is formed. For instance, Muller *et al*. developed a novel one-pot pyrrole synthetic method using the Paal-Knorr strategy.[43] According to this method 1,2,3,5-tetrasubstituted pyrroles (**12**) can be synthesized in good yields in a one-pot, three-step, four-component process by a coupling-isomerization-Stetter reaction-Paal-Knorr sequence of an electron-poor (hetero) aryl halide, (**9**) a terminal propargyl alcohol, (**10**) an aldehyde, (**11**) and a primary amine (**6**). The detailed course of the reaction constitutes the coupling of aryl substituted propargyl alcohol (**10**) with aryl halide (**9**) containing electron withdrawing group, spontaneous isomerization with the use of catalytic amount of $(Ph_3P)_2PdCl_2$ and CuI in the presence of boiling triethylamine that provides the formation of 1,4-enone skeleton (**13**) respectively. The 1, 4-addition of aldehyde (**11**) in the presence of thiazolium salt (**14**) (known as Stetter reaction) afford the 1, 4-dicarbonyl moiety required for the Paal-Knorr type cyclization with primary amine (**Scheme 3.3)**



Scheme 3.3 Four-component Stetter Paal-Knorr pyrrole synthesis

In 1890, Hantzsch published a brief note reporting that the reaction between ‘‘an equimolecular mixture of chloroacetone (**15**) and acetoacetic ester (**16**) under reflux in concentrated aqueous ammonia afforded a new compound, which he correctly identified as a pyrrole derivative (**17**) (**Scheme 3.4**).[44] The development of the so-called Hantzsch pyrrole synthesis has lagged far behind that of other classical name reactions, and until very recent developments it was far from being a general synthesis of polysubstituted pyrroles. Actually, Hantzsch synthesis is just the modification of the Feist-Benary synthesis of furans.[45-46]

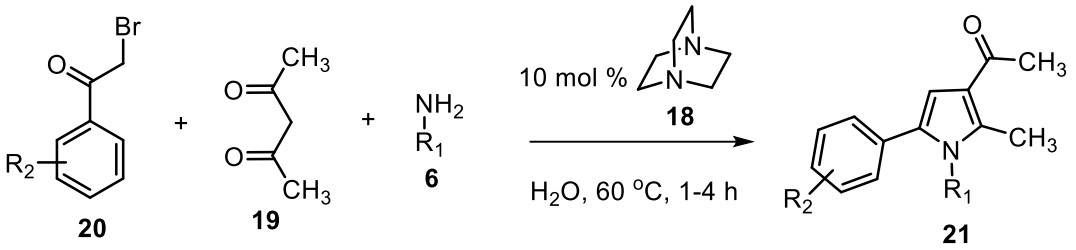


Scheme 3.4 The first multi-component pyrrole synthesis, reported by Hantzsch

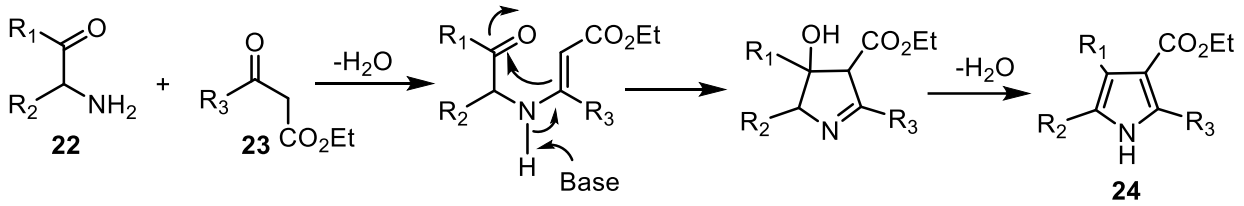
A base-catalyzed variation of the Hantzsch pyrrole (**21**) synthesis has been described by Meshram and coworkers using the organic base 1, 4-diazabicyclo [2.2.2] octane (DABCO) (**18**) as the catalyst and water as the reaction medium.[47] This method lacked generality since it was restricted to a single diketone substrate (**19**) and substitutions were limited to the positions 1 and 5, from variations in the primary amine (**6**) and phenacyl bromide components, (**20**) respectively (**Scheme 3.5**).

The most widely applied ring closure reaction method in the pyrrole chemistry was discovered by Knorr.[48] The reaction involves the condensation of an α-amino ketone (**22**) with a ketone (**23**) having a reactive methylene group alpha to the carbonyl group (**Scheme 3.6**). This method utilizes two components, the first one of which is the α-amino carbonyl component supplying the nitrogen and the carbon atoms at the second and third position of the pyrrole ring (**24**). The

second component supplies carbon atoms at the fourth and fifth position and must have a methylene protons with carbonyl group.

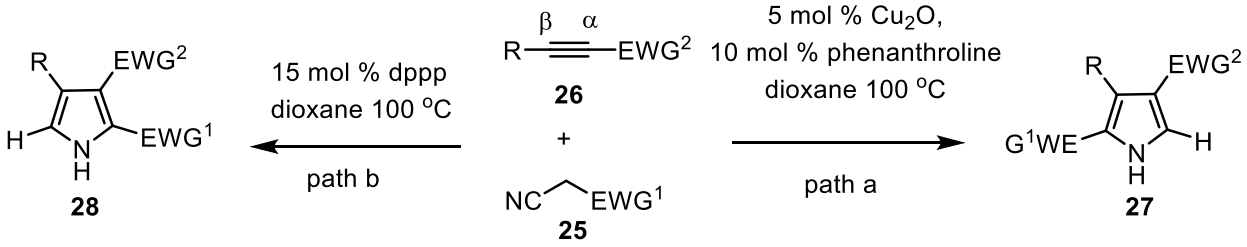


Scheme 3.5 Base-promoted Hantzsch pyrrole synthesis in water described by Meshram



Scheme 3.6 Knorr pyrrole synthesis

Yamamoto *et al.* reported that the copper-catalyzed reaction of isocyanides (**25**) with activated alkynes (**26**) produces the 2,4-di-EWG-substituted pyrroles (**27**) in good yields,[49] whereas the phosphine-catalyzed reaction of (**25**) with (**26**) affords the 2,3-di-EWG-substituted pyrroles (**28**) regioselectively (**Scheme 3.7**).[50] This interesting regio-reversal of the heteroaromatization stems from the region-differentiated addition of the nucleophilic isocyanide to activated alkynes (**25**), which is controlled by the catalyst species; the ordinary Michael addition of the metalated isocyanide to the *β*-carbon of (**26**) (path a) gives (**27**), while the addition of the nucleophilic isocyanide to the *α*-carbon attached to EWG^2 affords (**28**) (path b).

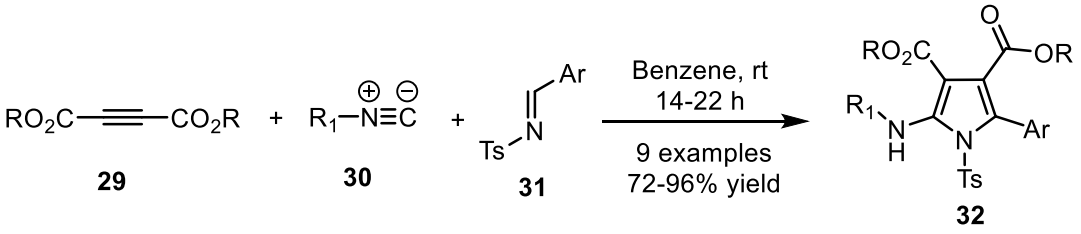


Scheme 3.7 Copper and phosphine catalyzed pyrrole synthesis

Due to their extensive applications in several fields, various other methods have been developed for the synthesis of pyrroles apart from these general methods such as cycloadditions,[51-53] metal-mediated reactions,[54-59] and several other methods.[60-63] Barring few indirect routes,[64-66] none of the methods offer direct access to substituted pyrrole-3-carboxaldehyde,[67] The direct

substitution at C-3 position of pyrrole,[68,70] particularly, direct formylation at C-3, remains a challenge because electrophillic substitutions mainly occurs at C-2 position. Therefore, a general strategy to synthesize pyrrole-3-carboxaldehyde from simple building blocks and a minimal number of overall synthetic steps is highly desirable. Additionally, it is also motivating to develop a new method with a variation where 1, 4-dicarbonyl compounds serve as source of three ring atoms and the other two atoms of the pyrrole moiety could be obtained from imines. This method will be different from Paal-Knorr which also involves 1, 4-dicarbonyl compounds. The organocatalytic cascade reactions involving two or more selective transformations using single/multiple catalysis, serve as powerful tools to conserve energy and minimize the number of synthetic operations.[71-74] With the idea of cascade synthesis for pyrroles in mind, we reasoned that a simple catalytic route for substituted pyrrole-3-carboxaldehydes could be developed from succinaldehyde and imines. Although, imines have been used earlier to synthesize pyrroles, there are several methods available in literature for pyrrole synthesis which directly involves preformed imines.

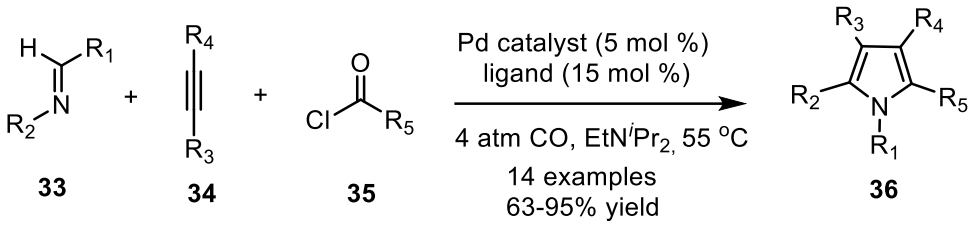
For example Nair and coworkers have developed a novel and efficient multi-component reaction of *N*-tosylimines (**31**), DMAD (**29**), and isocyanides (**30**) for the synthesis of 2-aminopyrrole systems (**32**) in excellent yields (**Scheme 3.8**).[75] It is interesting to note that 2-aminopyrroles have found use as synthetic precursors for acyclic nucleoside analogues of the pyrrolo-[2,3-*d*] pyrimidine ring system.[76]



29 30 31 32

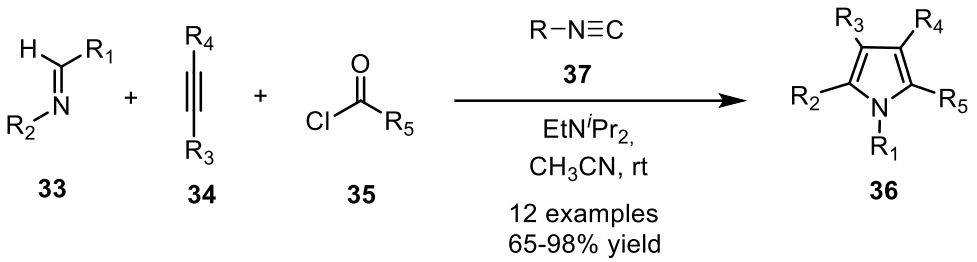
Scheme 3.8 Multi-component synthesis of 2-aminopyrroles from tosylimines and DMAD

Arndtsen and co-workers reported a new palladium-catalyzed method to prepare pyrroles (**36**) directly from three building blocks imines (**33**), alkynes (**34**), and acid chlorides (**35**) in good yield in almost all the cases as shown in (**Scheme 3.9**).[77] This approach provides a straightforward method to prepare pyrroles in one step and to diversify their structure by simple variations of any of the starting materials which occurs *via* complex series of eight individual steps.



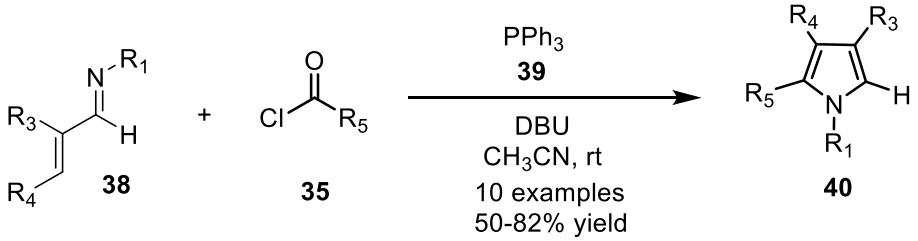
Scheme 3.9 Palladium catalyzed synthesis of pyrroles from imines, alkynes and acyl halides

In 2007 the same group has reported a direct approach towards the synthesis of pyrroles (**36**) from imines (**33**), acid chlorides (**34**), and alkynes (**35**) mediated by isocyanides (**37**). This reaction proceeds with wide range of each of these three substrates, providing a method to generate families of pyrroles in high yield. Mechanistic studies suggest this process proceeds via the generation of imino analogues of munchnones, which can undergo *in situ* coupling with alkynes to liberate isocyanate and form the pyrrole product as shown in (**Scheme 3.10**).[78]



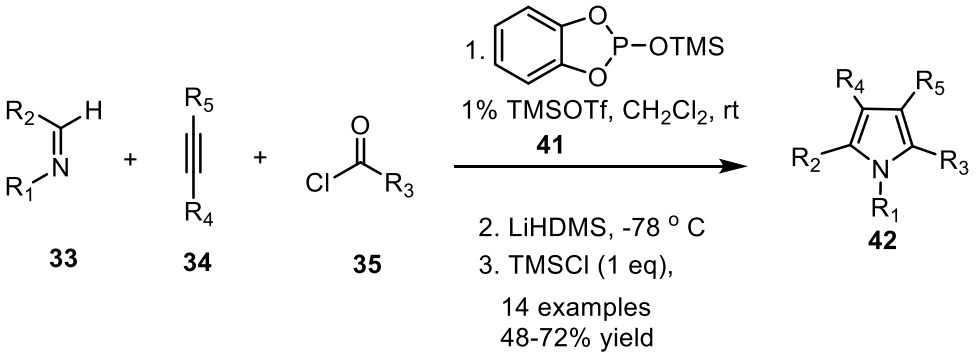
Scheme 3.10 Isocyanide-mediated pyrrole synthesis

A one-step method toward the synthesis of pyrroles (**40**) from *α, β*-unsaturated imines (**38**) and acid chlorides (**35**) has been developed. This reaction is mediated by triphenylphosphine (**39**), which eliminates phosphine oxide to allow cyclization yielding desired product in good yields as shown in (**Scheme 3.11**).[79] This reaction has been employed to access a diverse range of pyrroles *via* modulation of the two building blocks and applied as well to the synthesis of lukianol A.



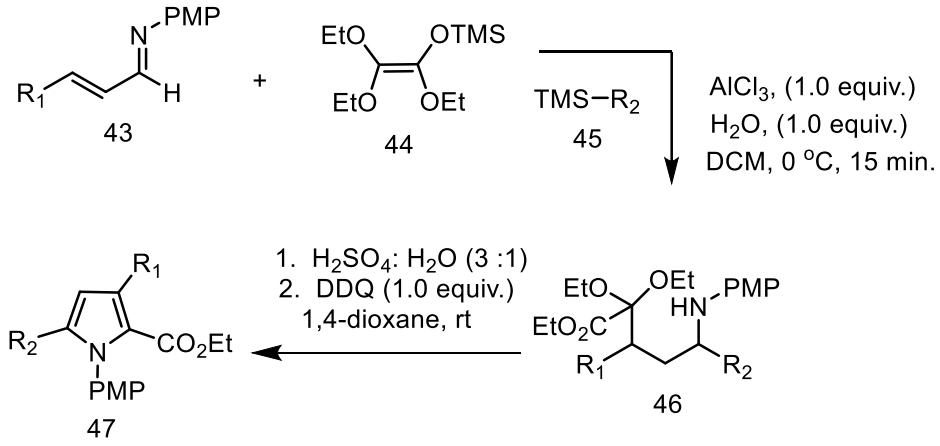
Scheme 3.11 Development of a PPh$_3$-mediated pyrrole synthesis

A one pot three component modular approach for the preparation of substituted pyrroles (**42**) by reaction between diverse range of imines, (**33**), acid chlorides (**35**) and [3+2] cycloaddtion with unsymmetrical alkynes (**34**) with high regioselectivity in the presence of phosphites (**41**) was reported as shown in (**Scheme 3.12**) with moderate yields.[80]



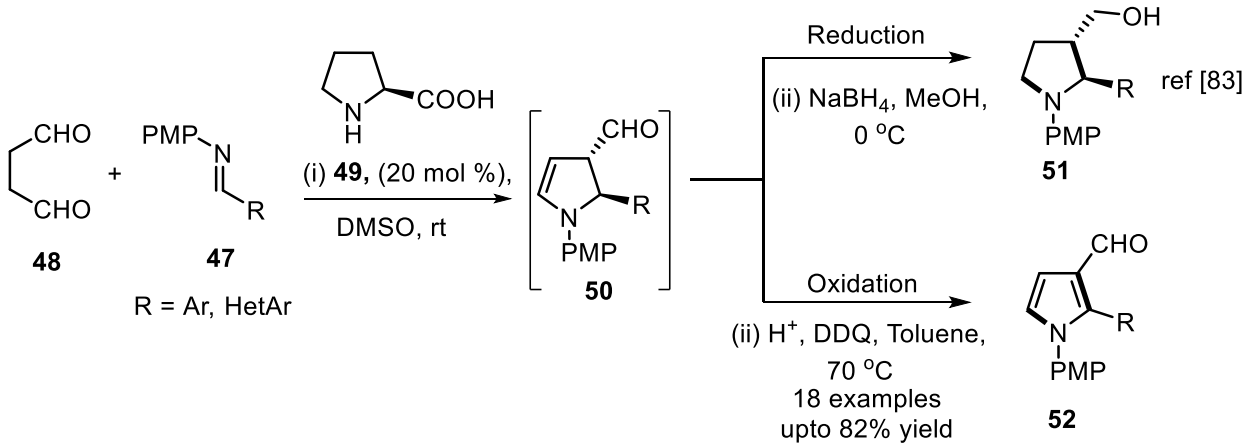
Scheme 3.12 Arndtsen's synthesis of pyrroles in the presence of phosphites

Shimizu and coworkers reported 2,3,5-trisubstituted pyrroles (**47**) in a regioselective manner using the double nucleophilic addition of *α, α*-dialkoxy ketene silyl acetals (44) and ketene sily thioacetals or trimethylsilyl cyanide (**45**) to *α, β*-unsaturated imines(**43**) followed by acid-promoted cyclization and oxidation with DDQ as shown in (**Scheme 3.13**).[81]



Scheme 3.13 Double nucleophilic addition to *α, β*-unsaturated imines

However, the use of easily available materials such as aldimines and succinaldehyde need to be explored further. Herein, we have developed entirely new synthetic method for the synthesis of substituted pyrrole-3-carboxyaldehdyes,(**52**) from easily available aldimines, (**47**) and 1,3-carbon *donor-acceptor* (D-A) precursor succinaldehye (**48**) which consists of following steps *viz*. direct Mannich reaction, acid catalyzed cyclization and DDQ mediated oxidative aromatization as two-pot two-steps sequence (**Scheme 3.14)**.[82]

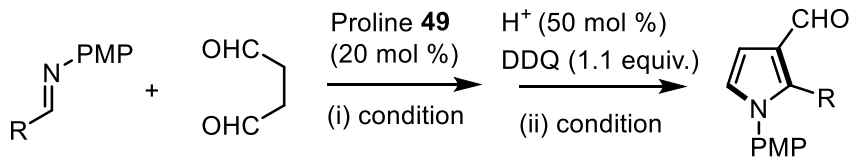


Scheme 3.14 Direct approaches towards substituted pyrrole-3-carboxyaldehdyes

3.5 Results and discussion

As part of our interest for the synthesis of heterocyclic compounds, we utilized aqueous solution of succinaldehyde (**48)**, a synthetically useful 1, 4-dicarbonyl unit, for the synthesis of pyrrolidines.[83] This formal [3+2] cycloaddition/annulations proceed through the *in situ* reduction of intermediate enamine (**50**). Next we envisioned that *in situ* oxidation of intermediate enamine (**50**) could lead to pyrrole (**52**). Having this idea in mind, we initiated the development of reaction conditions.[84,85] The optimization study for this direct approach to synthesize pyrrole-3-carboxaldehdye (**52**) were conducted using *N*-PMP aldimine**(47)** preformed from *p*-nitrobenzaldehyde as shown in (**Table 3.1**). During the initial experimental studies, we found that proline (**49)** catalyzed the direct Mannich reaction of aqueous succinaldehyde **(48)** with imine (**47)**, followed by acid catalyzed cyclization and DDQ mediated aromatization as two-steps sequence to afford substituted pyrrole 3-carboxaldehyde (**52)** in high yield (**entry 8, Table 3.1**). The amount of water present, alters the cause of reaction (**entry 6-8 and 10, Table 3.1**), similar to that of discussed earlier by Barbas and others for direct organocatalytic Mannich reaction.[86-88] Additionally, we also examined other solvent combinations (**entries 1-6, Table 3.1**) and found that DMSO/ toluene were optimal for this two-steps process. Furthermore, decreasing the catalyst loading (**entry 9, Table 3.1**) and under different catalytic system (**entry 12, Table 3.1**) led to prolonged reaction with reduced yield due to the lability of imine in the presence of water. The reaction proceeded with low yield in the absence of acid (**entry 11, Table 3.1**), which shows the presence of acid is essential for enhancing the rate of the intramolecular cyclization. Thus, we preferred to perform this two-step sequence with optimized conditions (**entry 8, Table 3.1**).

Table 3.1 Optimization of reaction conditions for the synthesis of (**52c**)[a]

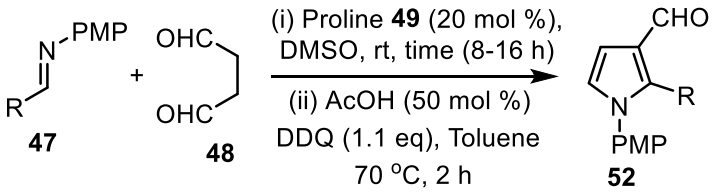


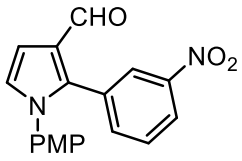
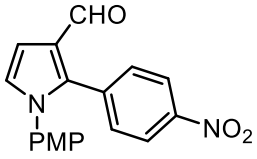
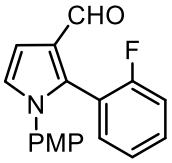
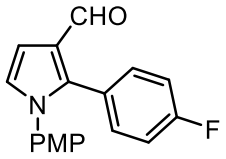
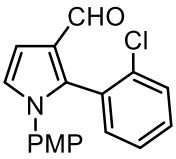
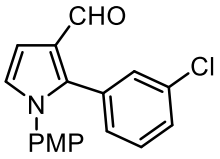
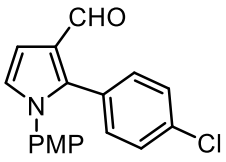
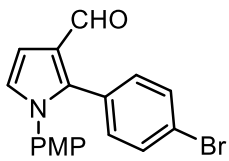
47 **48** **52**

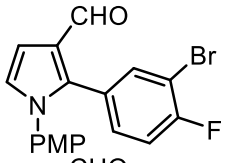
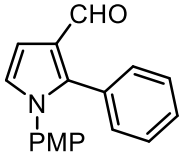
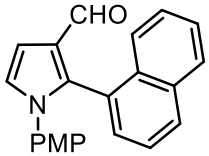
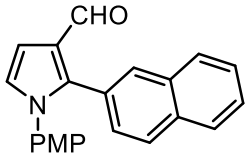
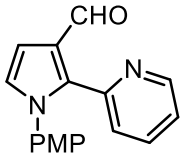
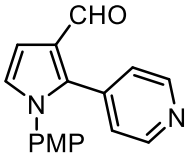
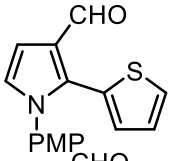
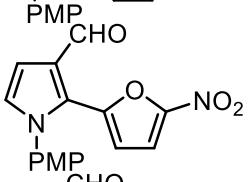
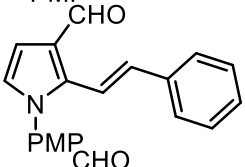
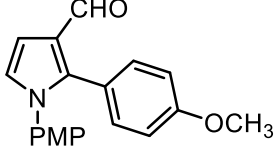
entry	3 (x M sol.)	steps	conditions[a]	Yield (%)[b]
1	6M	i	DMF, rt, 10 h	
		ii	DMF, rt, 24 h	<20
2	6M	i	DMF, rt, 10 h	
		ii	benzene, 40 ^{o}C, 6 h	51
3	6M	i	CH_3CN, rt, 12h	
		ii	CH_3CN, 40 ^{o}C, 6 h	34
4	6M	i	DMSO, rt, 9 h	
		ii	DMSO, 40 ^{o}C, 6 h	<20
5	6M	i	DMSO, rt, 9 h	
		ii	benzene, 40 ^{o}C, 6 h	54
6	6M	i	DMSO, rt, 9 h	
		ii	Toluene, 60 ^{o}C, 4 h	62
7	4M	i	DMSO, rt, 7 h	
		ii	Toluene, 60 ^{o}C, 4 h	73
8	**3M**	**i**	**DMSO, rt, 6 h**	
		ii	**Toluene, 70 ^{o}C, 2 h**	**82**
9[c]	3M	i	DMSO, rt, 10 h	
		ii	Toluene, 70 ^{o}C, 2 h	63
10	2M	i	DMSO, rt, 6 h	
		ii	Toluene, 70 ^{o}C, 2 h	65
11[d]	3M	i	DMSO, rt, 6 h	
		ii	Toluene, 70 ^{o}C, 2 h	49
12[e]	3M	i	DMSO, rt, 12 h	
		ii	Toluene, 70 ^{o}C, 2 h	43

[a](i) aldimine **47** (0.3 mmol), **48** (3M sol, 0.9 mmol), **49** (20 mol %), solvent (3.0 mL); (ii) CH_3CO_2H (50 mol %, 0.15 mmol), solvent (3.0 mL) DDQ (1.1 eq). [b]Isolated yields refer to **47** (after two-steps in one pot). [c]**49** (10 mol %). [d]CH_3CO_2H (not added). [e]pyrrolidine (20 mol %), CH_3CO_2H (20 mol %) were used in place of **49**.

Table 3.2 Substrate scope for the synthesis of substituted pyrroles from various imines[a]



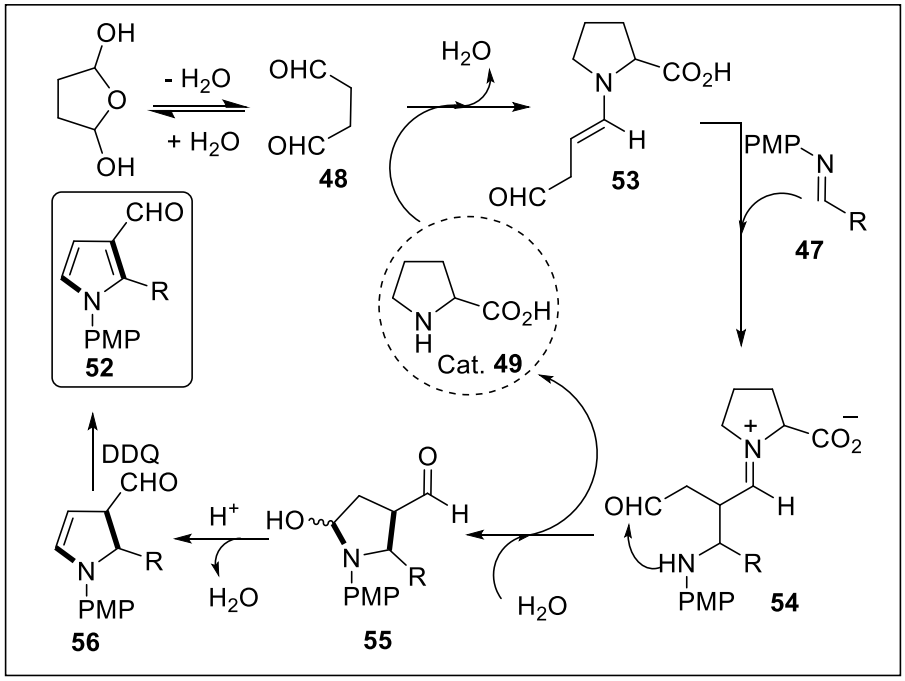
Entry	R	Product	52	% Yield[b]
1	3-NO_2-C_6H_4		**52a**	78
2	4-NO_2-C_6H_4		**52b**	82
3	2-F-C_6H_4		**52c**	71
4	4-F-C_6H_4		**52d**	76
5	2-Cl-C_6H_4		**52e**	69
6	3-Cl-C_6H_4		**52f**	74
7	4-Cl-C_6H_4		**52g**	77
8	4-Br-C_6H_4		**52h**	73

Entry	R	Product	52	% Yield[b]
9	3-Br,4-F-C_6H_3		**52i**	69
10	C_6H_5		**52j**	65
11	1-napthyl		**52k**	61
12	2-napthyl		**52l**	63
13	2-pyridyl		**52m**	72
14	4-pyridyl		**52n**	74
15	2-thienyl		**52o**	68
16	5-NO_2,2-furyl		**52p**	74
17	(E)CH=CHC_6H_5		**52q**	60
18	4-OCH_3-C_6H_4		**52r**	n.r

[a] (i) Imine **47** (0.3 mmol), **48** (3M sol, 0.9 mmol), **49** (20 mol %), DMSO (3.0 mL), (ii) Toluene (3.0 mL). [b] Time for Mannich reaction catalyzed by **49** (20 mol %).

With the optimal conditions in hand, we next examined the generality of this developed transformation by employing various *N*-PMP aldimines and the results are summarized in (**Table 3.2**). The reaction proceeded with high yields in case of electron-deficient arylimines (**entries 1-9, Table 3.2**). However, in cases of imines preformed from 2-substituted benzaldehydes (**entry 5, 6, Table 3.2**) and naphthaldehydes (**entry 11, 12, Table 3.2**), reactions were rather slow with lower yields, perhaps owing to steric crowding. Not only aryl imine but hetero-aryl imines too resulted in products with high yields (**entry 13-16, Table 3.2**), while the reactions with an alkenyl imine (**entry 17, Table 3.2**) and *in situ* generated imine from formaldehyde (**entry 18, Table 3.2**) were sluggish, resulted products in low yields. In case of electron-rich aryl imine and alkyl imine (**entry 19 and 20**, **Table 3.2**), the desired products were not obtained.

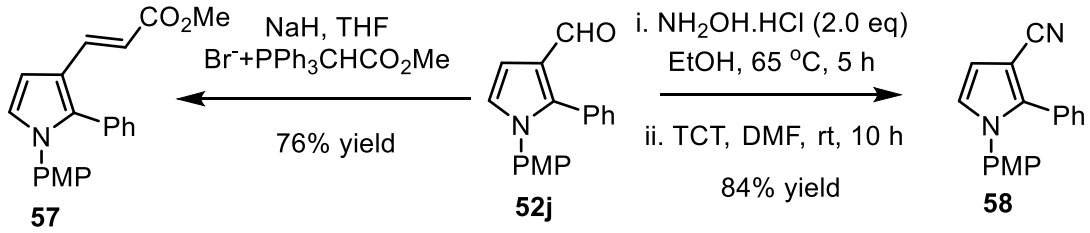
Based on our initial study and literature precedents on proline catalyzed Mannich reaction, the following stepwise mechanism is proposed to account for this reaction. As shown in (**Scheme 3.15**), the *in situ* generated enamine (**53**), generated from succinaldehyde (**48**) and proline (**49**), reacts with *N*-PMP aldimine (**47)** *via* a direct Mannich reaction to produce (**54**). The intermediate (**54**) undergoes intramolecular cyclization to hemiaminal (**56)** with the simultaneous regeneration of proline (**49**). Hemiaminal (**56**) underwent acid catalyzed dehydration and DDQ mediated aromatization to afford the substituted pyrrole 3-carboxaldehyde (**52**).



Scheme 3.15 Mechanism for two-steps synthesis of pyrrole-3-carboxaldehyde **52**

The resulting pyrrole-3-carboxaldehdyes (**52**) isolated by column chromatography and their structures were characterized by ^{1}H NMR, ^{13}C NMR, IR, and mass spectral data. The HRMS (ESI) spectrum of one of the compound (**52**) displayed a peak at 323.1060 for $[M+H]^{+}$ ion and a peak at 1660 cm^{-1} was observed for aldehydic C=O stretching in the IR spectrum. The ^{1}H NMR spectrum contained a characteristic singlet at δ ~ 3.82 (s, 3H), for $–OCH_3$ group, sharp doublet at δ ~ 6.89 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), for pyrrolic –CH protons, 9.73 (s, 1H), for aldehydic proton attached to pyrrole ring at C-3 position. A peak appeared at δ 55.48 and 186.01 ppm in ^{13}C NMR for $–OCH_3$ group and C=O of aldehyde group along with other carbons of **(52b)**. A representative ^{1}H and ^{13}C NMR of **(52b)** is shown in **Figure 3.3**.

The present two-steps protocol also works very well at preparative scale (2.0 mmol) of aldimines; resulting pyrroles (**52)** possessing the aldehyde functionality are important synthetic intermediates for further functionalization. A Wittig-reaction of (**52j**) provided the corresponding *α, β*-unsaturated ester **(57**) and trichloro-triazine (TCT) mediated dehydration[96] of *in situ* generated oxime from (**52j**) produced the corresponding nitrile compound (**58**) with high yields (**Scheme 3.16**).



Scheme 3.16 Synthetic transformation of pyrrole 3-carboxaldeyhde (**52j)**

3.6 Conclusions

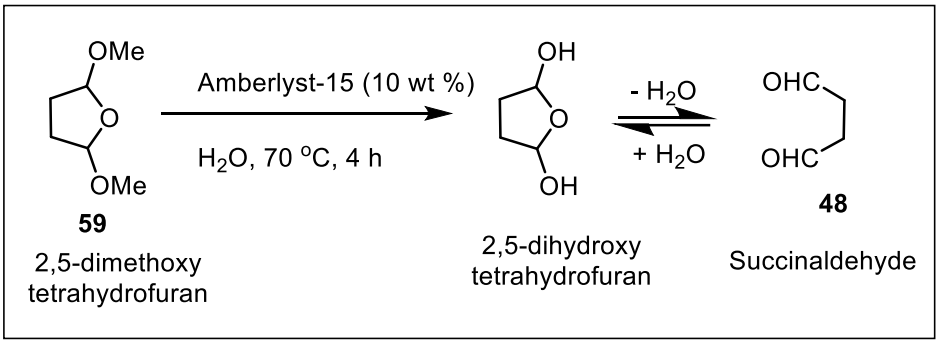
In conclusion, we have developed a new and direct method for the synthesis of substituted pyrrole-3-carboxaldehydes (**52**) from readily available precursors such as *N*-PMP aldimines (**47**) and succinaldehyde (**48**). The present two-pot protocol involves the organocatalytic Mannich reaction, intramolecular cyclization and oxidative aromatization as two-pot sequence under mild conditions. In general, this method provides a new entry to synthesize substituted pyrroles from 1, 4-dicarbonyl compounds, in addition to Paal-Knorr condensation.

3.7 General Experimental Methods

All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on SiO_2 gel F254 plates. The column chromatography was performed on silica gel (100-200 meshes) using a mixture of EtOAc/hexane as eluent. All other reagents were of analytical grade and used without further purification. ^1H 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 quadrupole electrospray ionization (ESI) technique.

3.8 Preparation of succinaldehyde 48 (3M solution)

To a stirred solution of 2, 5-dimethoxytetrahydrofuran **59** (2.0 g, 15.15 mmol) in H_2O (5.0 mL) was added Amberlyst-15 (10 wt %) and further heated at 70 ^oC for 4 h in an open flask. The resulting solution was cooled to rt and used directly for the said reaction.

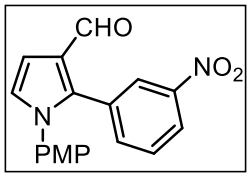


3.9 General procedure for the synthesis of pyrrole-3-carboxaldehydes (52) Succinaldehyde (**48)** (0.3 mL, 0.9 mmol, 3M solution) was added to a mixture of preformed *N*-PMP aldimine (**47)** (0.3 mmol) and L-proline (**49**) (7.0 mg, 0.06 mmol) in DMSO (3.0 mL) at room temperature. The reaction mixture was stirred at room temperature until the aldimine was consumed as monitored by TLC. The reaction was quenched with saturated $NaHCO_3$ solution (3 mL) and extracted with ethyl acetate (6 mL) with three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude adduct was taken in toluene (3 mL) and CH_3CO_2H (50 mol%, 9 μL) and then DDQ (75 mg, 0.33 mmol) was added. The reaction mixture was stirred and heated at 70 ^oC for 2 h and cooled to room temperature. The reaction was quenched with saturated $NaHCO_3$ solution (3 mL) and extracted with ethyl acetate (5 mL) twice and combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification

through silica gel column chromatography by eluting the mixture of EtOAc/hexane, gave pyrrole 3-carbxaldehydes (**52)** with good yields (58-82%). In almost all the cases, we also obtained about <10% initial starting aldehyde due to cleavage of corresponding imine under these conditions. The pure products were characterized based upon their spectroscopic data.

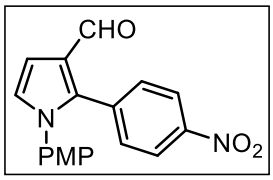
3.10 Analytical data of synthesized compounds (52a-52q)

1-(4-methoxyphenyl)-2-(3-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (52a)



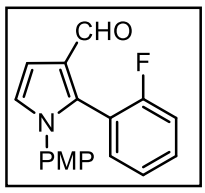
Yield (75 mg, 78%, semi-solid); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (s, 3H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 3.0 Hz, 1H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.41-7.49 (m, 2H), 8.01 (t, *J* = 1.4 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 9.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.51, 108.85, 114.65 (2C), 123.26, 124.97, 125.59, 125.82, 127.32 (2C), 129.29, 130.87, 131.15, 136.65, 138.27, 147.95, 159.33, 186.01; IR (KBr)/cm^{-1} 2920, 1746, 1680, 1244, 1172; HRMS (ESI): Calcd for $C_{18}H_{14}N_2O_4$ (MH^+) 323.1032; Found 323.1013.

1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (52b)



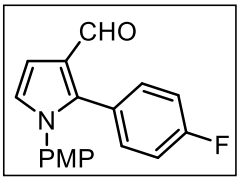
Yield (79 mg, 82%, pale yellow pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H), 9.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.48, 109.06, 114.63 (2C), 123.40 (2C), 125.17, 126.15, 127.13 (2C), 130.96, 131.60 (2C), 135.99, 138.24, 147.40, 159.30, 186.01; IR (KBr)/cm^{-1}2933, 1724, 1660, 1249, 1174; HRMS (ESI): Calcd for $C_{18}H_{14}N_2O_4$ (MH^+) 323.1032; Found 323.1060.

2-(2-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (52c)



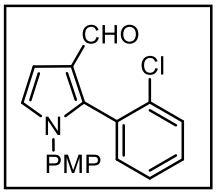
Yield(63 mg, 71%, gummy liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.78 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.93 (d, *J* = 3.0 Hz, 1H), 6.99-7.06 (m, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 1.6 Hz, 1H), 7.24-7.27 (m, 1H), 7.34-7.36 (m, 1H), 9.61 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.43, 108.01, 114.23 (2C), 115.06, 115.90, 116.07, 124.05, 125.31, 126.57 (2C), 131.23, 131.79, 133.23, 135.79, 158.98, 161.23, 186.36; IR (KBr)/cm^{-1}2908, 1730, 1680, 1247, 1174; HRMS (ESI): Calcd for $C_{18}H_{14}FNO_2$ (MH^+) 296.1087; Found 296.1094.

2-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (52d)



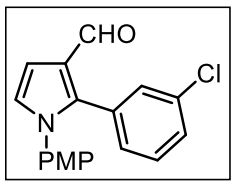
Yield (67 mg, 76%, gummy liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.81 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 3.0 Hz, 1H), 6.86 (d, *J* = 3.0 Hz, 1H), 6.97-7.02 (m, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.17 (dd, *J* = 8.8 Hz, 4.9 Hz, 2H), 9.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.43, 107.83, 114.35 (2C), 115.37, 115.55, 124.51, 124.96 (2C), 127.12 (2C), 131.50, 132.69 (2C), 141.07, 158.94, 163.74, 186.65; IR (KBr)/cm^{-1}2912, 1726, 1672, 1249, 1170; HRMS (ESI): Calcd for $C_{18}H_{14}FNO_2$ (MH^+) 296.1087; Found 296.1070.

2-(2-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (52e)



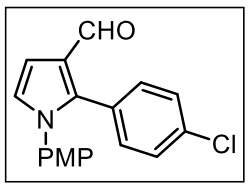
Yield (64 mg, 69%, gummy liquid); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 3.0 Hz, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.28-7.32 (m, 2H), 7.35-7.37 (m, 2H), 9.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.42, 107.66, 114.17 (2C), 114.84, 122.81, 124.75, 125.12, 126.56 (2C), 129.80, 130.59, 131.56, 133.50, 135.42, 139.00, 158.88, 186.30; IR (KBr)/cm^{-1}2918, 1726, 1680, 1246, 1172; HRMS (ESI): Calcd for $C_{18}H_{14}ClNO_2$ (MH^+) 312.0791; Found 312.0798.

2-(3-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (52f)



Yield (69 mg, 74%, semi-solid); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.90 (d, *J* = 3.0 Hz, 1H), 7.04 (d, *J* = 8.0 Hz, 2H), 7.07 (d, *J* = 1.6 Hz, 1H), 7.23-7.28 (m, 2H), 8.32 (d, *J* = 8.0 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.44, 107.91, 114.38 (2C), 124.67, 125.29, 127.04 (2C), 128.67, 129.03, 129.46, 130.81, 131.03, 131.27, 134.16, 140.30, 158.97, 186.58; IR (KBr)/cm^{-1}2920, 1714, 1666, 1246, 1173; HRMS (ESI): Calcd for $C_{18}H_{14}ClNO_2$ (MH^+) 312.0791; Found 312.0792.

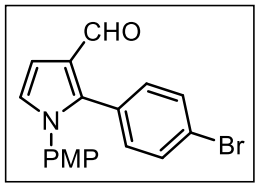
2-(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (52g)



Yield (72 mg, 77%, gummy liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 3.4 Hz, 1H), 6.87 (d, *J* = 3.4 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.27 (d, *J* = 8.5 Hz, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.47, 108.09,

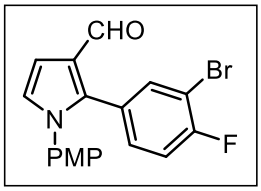
114.44 (2C), 122.74, 123.09, 124.55, 125.26, 127.13 (2C), 128.24, 131.55(2C), 132.37 (2C), 140.68, 159.01, 186.63; HRMS (ESI): Calcd for $C_{18}H_{14}ClNO_2$ (MH^+) 312.0791; Found 312.0789.

2-(4-bromophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (52h)



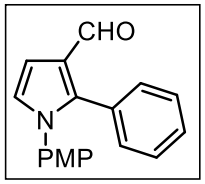
Yield (78 mg, 73%, amorphous solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 3.2 Hz, 1H), 6.87 (d, *J* = 3.2 Hz, 1H), 6.99 (, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.6 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.15, 107.78, 114.13 (2C), 122.43, 122.77, 124.24, 124.95, 126.81 (2C), 127.92, 131.23 (2C), 132.06 (2C), 140.36, 158.70, 186.31; IR (KBr)/cm^{-1}2914, 1714, 1668, 1248, 1178; HRMS (ESI): Calcd for $C_{18}H_{14}BrNO_2$ (MH^+) 356.0286; Found 356.0295.

2-(3-bromo-4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (52i)



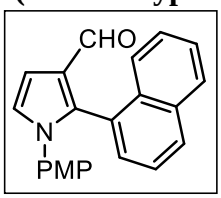
Yield (77 mg, 76%, slightly yellow semi-solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, *J* = 3.0 Hz, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 3.0 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.03-7.09 (m, 1H), 7.45 (dd, *J* = 6.6 Hz, 2.0 Hz, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.49, 108.15, 114.50 (2C), 116.26, 116.48, 124.74, 125.29, 127.16 (2C), 131.13, 131.52, 135.87, 199.08, 157.86, 159.14, 160.35, 186.26; IR (KBr)/cm^{-1}2910, 1714, 1681, 1246, 1181; HRMS (ESI): Calcd for $C_{18}H_{13}BrFNO_2$ (MH^+) 374.0192; Found 374.0235.

1-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrole-3-carbaldehyde (52j)



Yield (54 mg, 65%, pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 3.2 Hz, 1H), 6.87 (d, *J* = 3.2 Hz, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 7.18-7.20 (m, 2H), 7.28-7.32 (m, 3H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.36, 107.60, 114.21 (2C), 124.37, 124.91, 127.01 (2C), 128.19 (2C), 128.46, 129.16, 130.91 (2C), 131.65, 142.42, 158.76, 187.06; IR (KBr)/cm^{-1} 2912, 1710, 1672, 1244, 1174; HRMS (ESI): Calcd for $C_{18}H_{15}NO_2$ (MH^+) 278.1181; Found 278.1200.

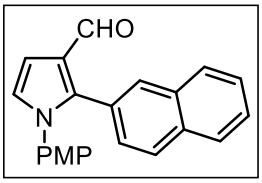
1-(4-methoxyphenyl)-2-(naphthalene-1-yl)-1*H*-pyrrole-3-carbaldehyde (52k)



Yield (60 mg, 61%, amorphous solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 6.60 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 3.2 Hz, 1H), 7.00 (d, *J* =3.2 Hz, 2H), 7.37-7.45 (m, 4H), 7.59 (d, *J* = 8.0 Hz, 1H),

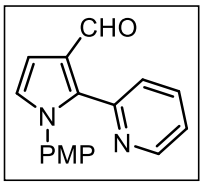
7.82 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.1Hz, 1H), 9.38 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.32, 107.51, 114.06 (2C), 124.83, 125.62, 125.97(2C), 126.25 (2C), 126.92, 127.11 (2C), 128.26, 129.63, 130.43, 131.88, 133.32, 133.44, 140.87, 158.63, 186.87; HRMS (ESI): Calcd for $C_{22}H_{17}NO_2$ (MH^+) 328.1337; Found 328.1335.

1-(4-methoxyphenyl)-2-(naphthalene-2-yl)-1*H*-pyrrole-3-carbaldehyde (52l)



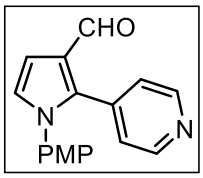
Yield (62 mg, 63%, amorphous solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 3.2 Hz, 1H), 6.92 (d, *J* = 3.2 Hz, 1H), 7.04 (d, *J* = 8.8 Hz, 2H), 7.13 (d, *J* = 8.5 Hz, 1H), 7.50-7.52 (m, 2H), 6.70 (d, *J* = 8.3 Hz, 1H), 7.79-7.83 (m, 3H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.27, 107.51, 114.03 (2C), 124.82, 125.58, 125.92, 126.22 (2C), 126.89, 127.07 (2C), 128.24, 129.62, 130.40, 131.85, 133.30, 133.42 (2C), 140.91, 158.62, 186.88; IR (KBr)/cm^{-1}2922, 1715, 1668, 1248, 1172; HRMS (ESI): Calcd for $C_{22}H_{17}NO_2$ (MH^+) 328.1337; Found 328.1311.

1-(4-methoxyphenyl)-2-(pyridine-2-yl)-1*H*-pyrrole-3-carbaldehyde (52m)



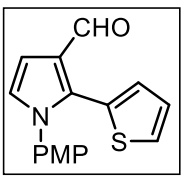
Yield (60 mg, 72%, semi-solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.85-6.91 (m, 2H), 7.01-7.09 (m, 3H) 7.20 (m, 1H), 7.54-7.58 (m, 1H), 8.60 (d, *J* = 4.6 Hz, 1H), 9.92 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.44, 108.14, 114.35 (2C), 120.95, 122.63, 125.55, 125.79, 126.94 (2C), 131.97, 135.89, 139.76, 149.12, 149.68, 158.96, 187.65; HRMS (ESI): Calcd for $C_{17}H_{14}N_2O_2$ (MH^+) 279.1133; Found 279.1223.

1-(4-methoxyphenyl)-2-(pyridine-4-yl)-1*H*-pyrrole-3-carbaldehyde (52n)



Yield (62 mg, 74%, semi-solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 3.2 Hz, 1H), 6.94 (d, *J* = 3.2 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 4.6 Hz, 2H), 8.55 (d, *J* = 4.6 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.51, 109.04, 114.65 (2C), 125.25, 125.38 (2C), 126.31, 127.12 (2C), 130.94, 137.53, 138.04, 149.06 (2C), 159.37, 186.04; HRMS (ESI): Calcd for $C_{17}H_{14}N_2O_2$ (MH^+) 279.1133; Found: 279.1140.

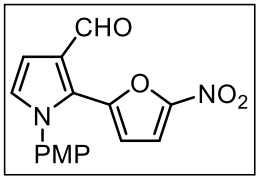
1-(4-methoxyphenyl)-2-(thiophen-2-yl)-1*H*-pyrrole-3-carbaldehyde (52o)



Yield (58 mg, 68%, gummy liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 3.5 Hz, 1H), 6.96 (d, *J* = 3.5 Hz, 1H), 7.08 (m, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 5.0 Hz, 1H), 9.75 (s,

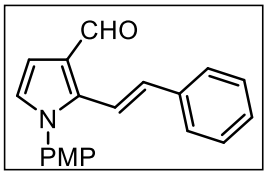
1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.50, 107.90, 114.28 (2C), 125.46, 125.71, 127.05, 127.58 (2C), 128.42, 129.57, 130.55, 131.50, 131.48, 159.34, 186.76; HRMS (ESI): Calcd for $C_{16}H_{13}NO_2S$ (MH^+) 284.0755; Found 284.0749.

1-(4-methoxyphenyl)-2-(5-nitrofuran-2-yl)-1*H*-pyrrole-3-carbaldehyde (52p)



Yield (69 mg, 74%, semi-solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.21 (d, *J* = 3.8 Hz, 1H), 6.85 (d, *J* = 3.5 Hz, 1H), 6.90 (d, *J* = 3.5 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 2H), 7.16 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 3.8 Hz, 1H) 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.67, 110.04, 111.70, 112.65, 112.82, 114.83 (2C), 118.68, 127.70 (2C), 128.15, 134.17, 147.14, 151.00, 160.28, 186.22; HRMS (ESI): Calcd for $C_{16}H_{12}N_2O_5$ (MH^+) 313.0824; Found: 313.0833.

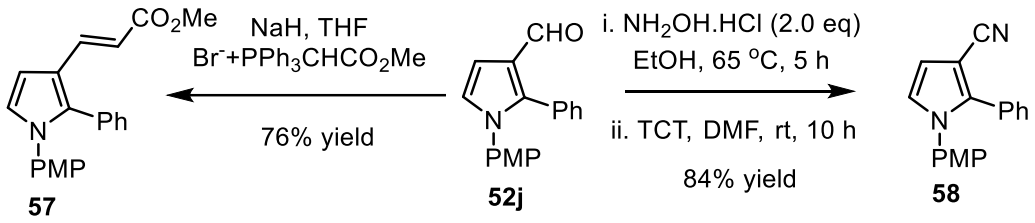
(*E*)-1-(4-methoxyphenyl)-2-styryl-1*H*-pyrrole-3-carbaldehyde (52q)



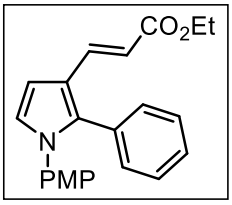
Yield (54 mg, 60%, pasty liquid); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.75 (bs, 2H), 6.81-6.85 (m, 1H), 6.90-6.93 (m, 3H), 7.19-7.23 (m, 4H), 7.27-7.31 (m, 3H), 9.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.60, 109.81, 114.66 (2C), 115.73, 124.37, 125.04, 126.75 (2C), 127.39 (2C), 128.43, 128.76 (2C), 131.76, 135.52, 136.58,138.93, 159.49, 186.00; HRMS (ESI): Calcd for $C_{20}H_{17}NO_2$ (MH^+) 304.1337; Found 304.1306.

3.11 Experimental procedure for the synthesis of (*E*)-Methyl 3-(1-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrol-3-yl)acrylate (**57**)

To a stirred solution of phosphonium bromide (330 mg, 0.79 mmol) in dry THF (3 mL) was added NaH (0.032 mg, 0.79 mmol, 60% in oil) in portions at rt and further stirred for 30 min at the same temperature. The solution of compound (**52j**) (200 mg, 0.71 mmol) in THF (2 mL) was added to this stirred mixture at 0 ^{o}C and further stirred at rt for overnight. After usual work-up, the crude material was passed through a small silica gel column gave compound (**57**) as pasty liquid (182 mg, 76% yield) as shown in (**Scheme 3.16A)**.



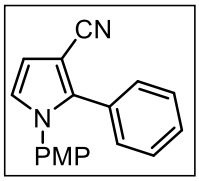
Scheme 3.16A Synthetic transformations of pyrrole 3-carboxaldeyhde (**52j)**



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 3.85 (s, 3H), 6.38 (d, *J* = 14.2 Hz, 1H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 3.2 Hz, 1H), 6.87 (d, *J* = 3.2 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 7.19-7.35 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.28, 55.31, 107.56, 113.21, 114.78 (2C), 124.28, 124.78, 124.85 (2C), 126.95 (2C), 128.06, 128.29, 129.11, 131.86, 132.55, 141.27, 146.34, 158.66, 168.56; HRMS (ESI): Calcd for $C_{21}H_{19}NO_3(MH^+)$ 334.1443; Found 334.1445.

3.12 Synthesis of 1-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrole-3-carbonitrile (**58**)

To a stirred solution of (**52j**) (250 mg, 0.9 mmol) in EtOH (5 mL) was added $NH_2OH.HCl$ (0.12 g, 1.8 mmol) and further refluxed for 5 h. The reaction was cooled to rt and solvent was removed under reduced pressure. The resulting mixture was further extracted between EtOAc (10 mL) and H_2O (6 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure results crude oxime, which was used further without purification. In a separate flask, 2,4,6-Trichloro-[1,3,5]triazine (TCT) (1.83 g, 10.0 mmol) was added to DMF (2 mL),and stirred at rt until a white solid forms. Then crude oxime solution in DMF (3 mL) was added, the mixture was stirred at room temperature, monitored (TLC) until completion (10 h). Water (2 mL) was added then extracted twice with ethyl acetate. The combined organic layer was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude material was purified through a small pad of column giving compound (**58**) as slight yellow liquid (207 mg, 84% yield) as shown in (**Scheme 3.16A)**.



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 3.2 Hz, 1H), 6.86 (d, *J* = 3.2 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 7.25-7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 97.34, 108.20, 114.28 (2C), 124.32 124.86, 127.21 (2C), 128.03, 128.34 (2C), 129.08, 130.87 (2C), 131.08, 142.22, 158.73; HRMS (ESI): Calcd for $C_{18}H_{14}N_2O$ (MH^+) 275.1184; Found 275.1168.

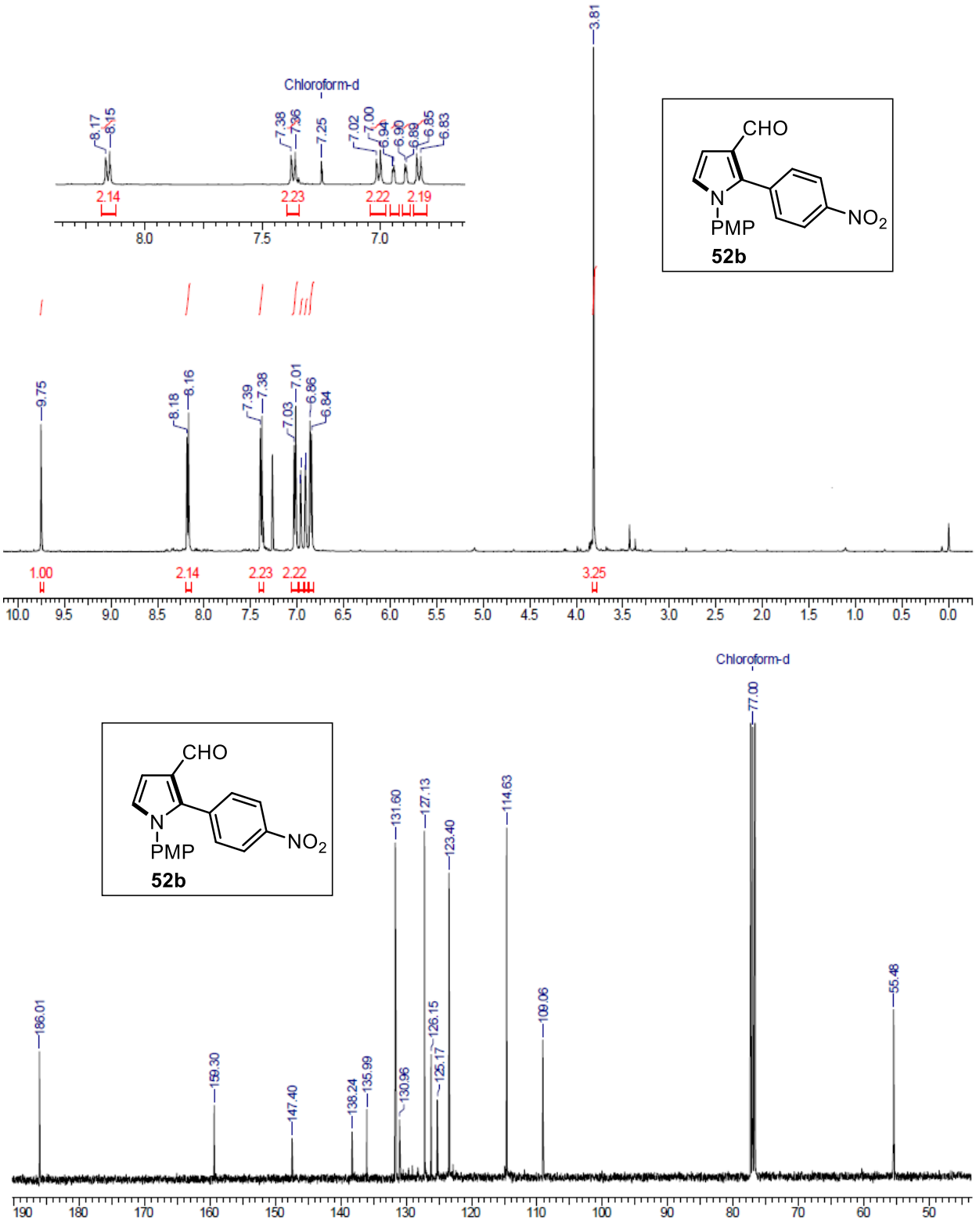


Figure 3.3 ^{1}H and ^{13}C NMR spectra of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrole-3-carbaldehyde (**52b**)

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Chapter III

PART-II: Proline catalyzed one-pot multicomponent synthesis of substituted-3-formyl pyrroles

3.14 Introduction

From the standpoint of green chemistry, development of organic transformations for the construction of bioactive heterocyclic scaffolds in reduced number of synthetic steps with high molecular complexity and diversity is an everlasting demand in organic chemistry. Tandem reactions are one of the finest choices which is defined as a consecutive series of intramolecular organic reactions which often proceeds *via* highly reactive intermediates.[1-2] This can be comprehended for chemical reactions as two or more reactions which follow one another. They are also termed as cascade or domino processes in which several bonds are formed in a sequence without isolating intermediates, changing reaction conditions or adding reagents. In other words, these are a class of reactions where the sequential transformation of the substrate occurs *via* two or more mechanically distinct processes.

The major advantages of tandem reactions are that they are often fast due to its intramolecular nature, avoid isolation of intermediates whereby reduces the labor and time required for the given target molecules, reduce the waste generation, displays high atom economy, build a large number of complexity in effectively single step, low environmental impact that is use of environmentally friendly solvents.

3.15 Multi-component reactions

One-pot multicomponent reactions (MCRs) have recently gained a considerable and steadily increasing academic, economic, and ecological interest because they address very fundamental principles of synthetic efficiency and reaction design. One of the best-studied method in the sustainable and diversity-oriented synthesis of small ring heterocycles which plays an important role in modern synthetic chemistry. These reactions allow construction of novel libraries of a small sized drug-like molecules with structural diversity such as functional chromophores, pharmaceutically active compounds, and marine alkaloids.[3-16] Multi-component reactions (MCRs), where three or more easily accessible compounds react together in a single step to form a product displaying features of all inputs without isolating the intermediate have become an important tool for generating organic compounds with a high degree of molecular diversity.[17-19] MCRs play an important role in modern synthetic chemistry and offer significant advantages over conventional multi-step syntheses.[20-22] These reactions have broad substrate scope and capability to tolerate diverse functionalities.

Literature is flooded with the articles of MCRs which show their potency in the synthetic field. Among them the most studied classical MCRs are Strecker synthesis,[23] Mannich reaction,[24] Robinsons synthesis of tropinone,[25] Ugi reaction,[26] Biginelli reaction,[27] Passerini reaction,[28] Pictet-Spengler reaction,[29] organometallic multi-component reactions,[30] Hantzsch dihydropyridine synthesis[31] and Hantzsch pyrrole synthesis [32] which are described in the below mentioned (**Figure 3.4**).

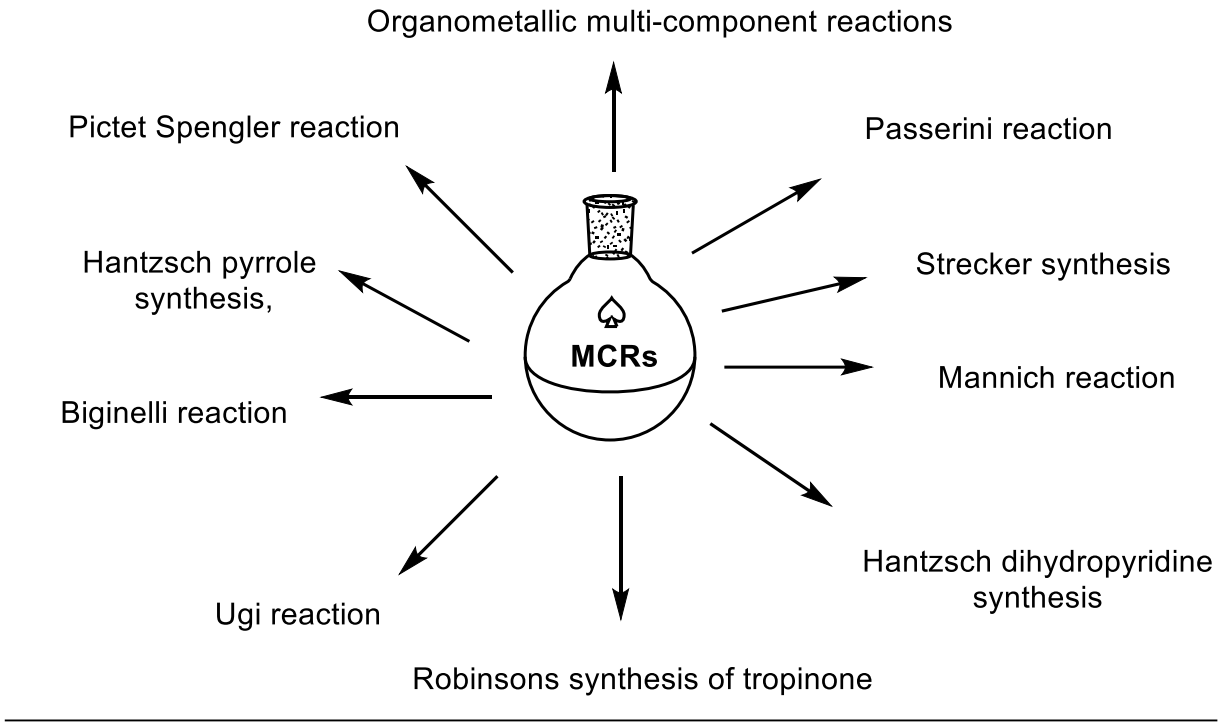
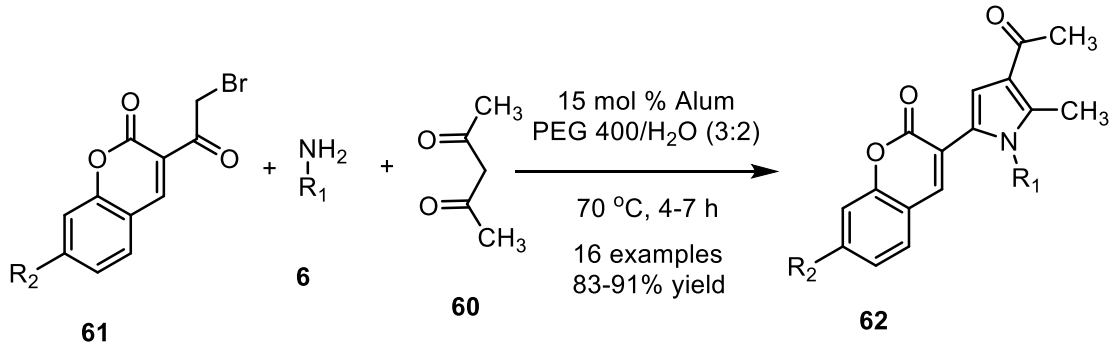


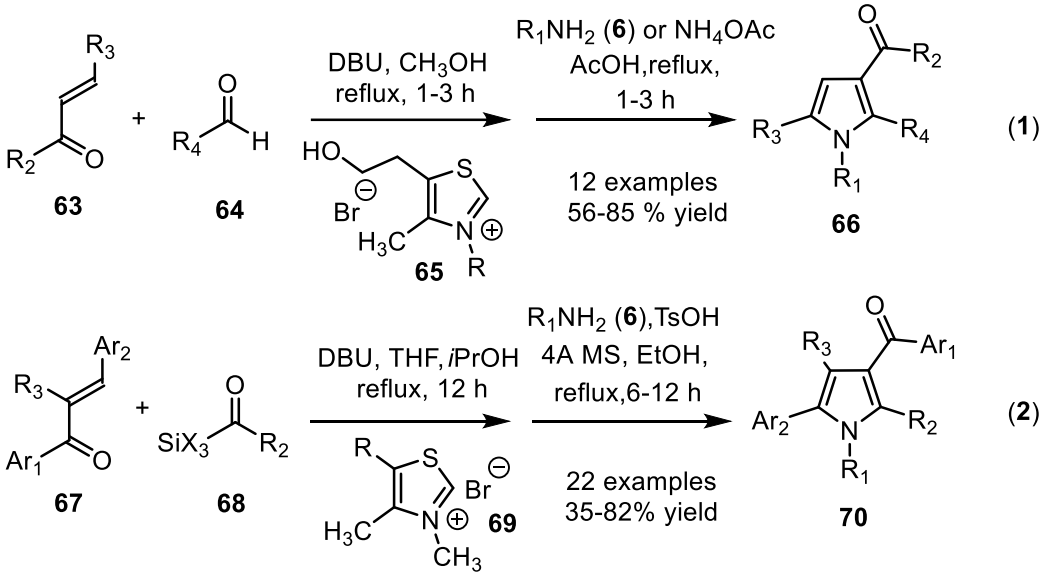
Figure 3.4 Representation of a various one-pot multi-component name reactions

In this fashion, the unprecedented blossom of reports has been published on MCRs which delivered either potential bioactive motifs in a reduced number of synthetic steps or new libraries for biological screenings. In addition, there are several articles where these multi-component reactions are amalgamated with other valuable C−C as well as C−heteroatom bond forming reactions in a domino sequence to access complex structures in a single step.[33-34] Particularly, synthesis of diverse substituted pyrroles involving one-pot multi-bond approaches such as multi-component reactions, cascade reactions, and one-pot synthetic sequences is a useful tool for the synthesis of complex molecules in a single step. A number of novel methodologies have been established to generate diverse substituted pyrrole scaffolds *via* multicomponent approach.[35-36]

For example, a three-component Hantzsch synthesis of pyrroles (**62**) from primary amines (**6**), 2,4-pentanedione (**60**) and 3-(bromoacetic)-coumarin derivatives (**61**) has been reported by Das and coworkers (**Scheme 3.17**).[37] The pyrrole derivatives thus obtained were designed to contain a coumarin moiety, which was considered of interest in view of its pharmacological importance. The reaction was catalyzed by alum($AlK(SO_4)_2.12H_2O$), an eco-friendly catalyst, which requires an aqueous reaction medium. In this case, the reaction was carried out in a mixture of water and polyethyleneglycol, which provides a micellar environment for the reaction to take place. Al^{3+} was identified as the active Lewis acidic species that promoted both the enaminone formation and the polarization of the C–Br bond needed to facilitate the first step of the Hantzsch reaction.



Scheme 3.17 Alum-promoted Hantzsch pyrrole synthesis in polyethyleneglycol–water

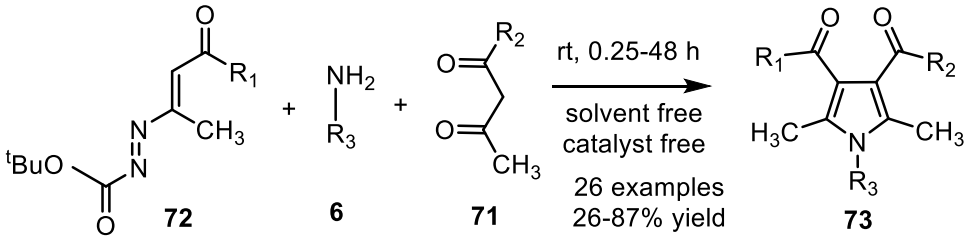


Scheme 3.18 Synthesis of pyrroles based on a Stetter and sila-Stetter /Paal–Knorr sequence

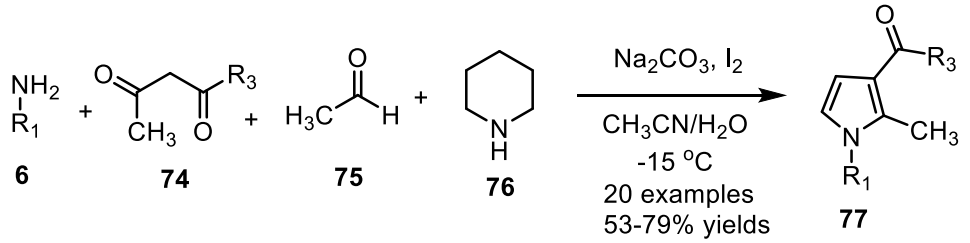
Jing group developed an efficient method for the synthesis of highly complex phenyl and heterocycle substituted pyrroles from pre-synthesized *α, β*-unsaturated ketones (**63**) and using

DBU as abase. Thiazolium (**65**) catalyzed Stetter reaction of the latter with aldehydes (**64**) generates 1,4-diketone intermediates, and the sequential addition of primary amines(**6**) leads to the desired pyrrole products (**66**) (**Eqn 1, Scheme 3.18**).[38] Later on, Scheidt group reported the combination of sila-Stetter and Paal–Knorr reactions[39,40] for the synthesis of polysubstituted pyrroles (**70**). In this case, the starting materials employed were chalcones (**67**) and acylsilanes (**68**) instead of aldehydes (**64**), in the presence of thiazolium catalyst (**69**) and the first reaction requires the addition of isopropyl alcohol. Also, this process differs from the previous one in the addition of *p*-toluenesulfonic acid and 4 Å molecular sieves in order to facilitate the Paal–Knorr reaction (**Eqn 2, Scheme 3.18**).

Attanasi *et al.* reported new and efficient synthesis of polysubstituted pyrroles (**73**) by a sequential one-pot three-component reaction between primary aliphatic amines (**6**), active methylene compounds (**71**), and 1,2-diaza-1,3-dienes (DDs) (**72**). The reactions were performed without catalyst and under solvent-free conditions with complete control of pathway selectivity. Notably, the ready availability of the starting materials and the high level of practicability of the reaction and work up make this approach an attractive complementary method for access to unknown polysubstituted pyrroles (**Scheme 3.19**).[41]



Scheme 3.19 Synthesis of pyrroles from aliphaticamines, 1,3-dicarbonyl compounds

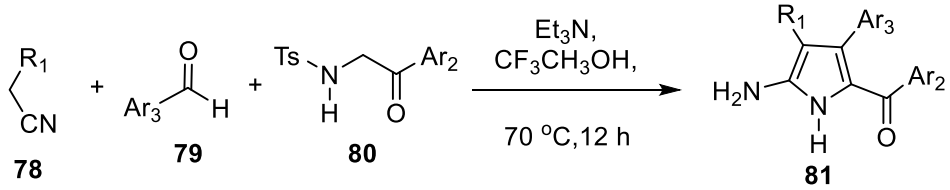


Scheme 3.20 Iodocyclization mediated multi-component 1, 2, 3-trisubstituted pyrrole synthesis

Zeng *et al.* has described a novel and efficient methodology for the synthesis of 1,2,3-trisubstituted pyrroles (**77**) by one-pot two-step reaction from primary amines (**6**), dicarbonylcompounds (**74**), acetaldehyde (**75**) and piperidine (**76**) (**Scheme 3.20**).[42] The

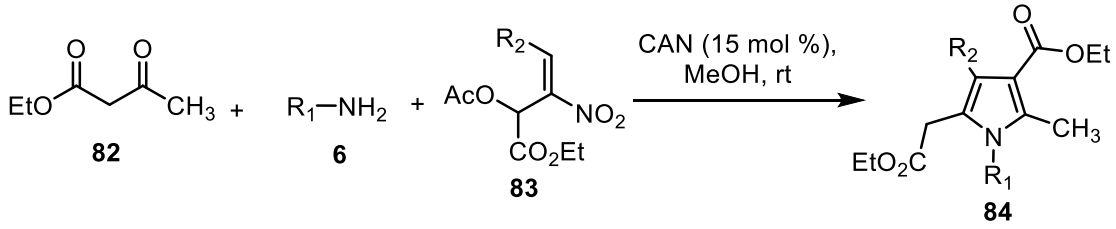
iodocyclization of a series of *β*-enamino esters followed by dehydroiodination, led to the formation of corresponding pyrroles. This approach provides an easy access to a wide range of 1,2, 3-trisubstituted pyrroles in good yields.

A very efficient synthesis of derivatives of the 2-amino-5- ketoarylpyrrole scaffold, (**81**) which has been developed by Wang and Domling (**Scheme 3.21**).[43] A mixture of *N*-protected *α*-amino acetophenones, (**80**) aromatic aldehydes (**79**) and malonodinitrile, cyanoacetic acid or cyanoacetamides, (**78**) after 12 hours of reflux in trifluoroethanol, was found to give pyrroles as solids that precipitated from the reaction mixture, thus avoiding the need for chromatography.

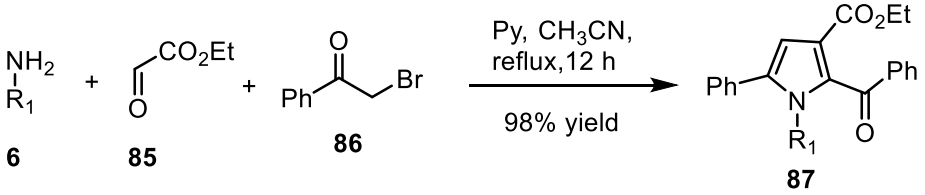


Scheme 3.21 Domling's three-component synthesis of 2-acylpyrroles

Chen and coworkers developed multi-component reaction from amines, (**6**) ethyl acetoacetate (**82**) and nitroallylic acetates, (**83**) catalyzed by ceric ammonium nitrate (CAN), for the synthesis of N-protected pyrrole diethyl 2, 4-dicarboxylate derivatives (**84**) (**Scheme 3.22**).[44]



Scheme 3.22 CAN catalyzed three-component synthesis of pyrroles

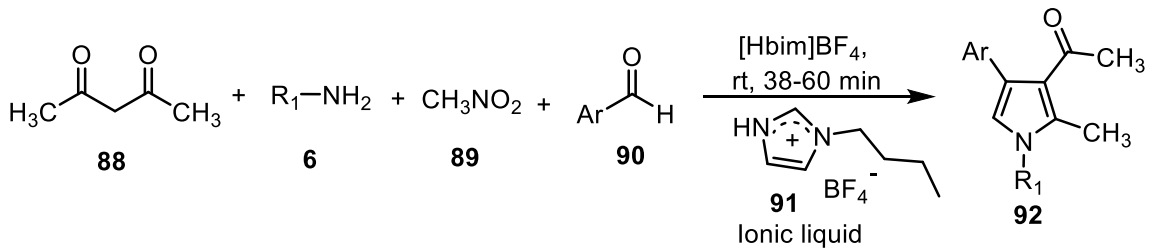


Scheme 3.23 Base promotedfour-component synthesis of 2-acylpyrroles

Wang and coworkers reported a straight forward route to 1,2,3,5-tetrasubstituted pyrroles (**87**) which is based on a four-component reaction in refluxing acetonitrile among primary amines, (**6**) ethyl glyoxylate (**85**) and two equivalents of 2-bromoacetophenones (**86**) in the presence of

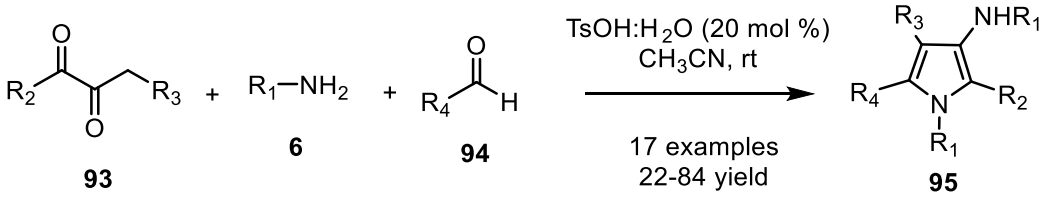
pyridine as a basic catalyst (**Scheme 3.23)**.[45] This transformation involves the creation of four bonds by the assembly of [2+1+1+1] atom fragments.

The group of Meshram has recently described a ‘‘catalyst free’’ four-component synthesis of pyrroles using a reusable ionic liquid as reaction medium. Coupling of 1, 3-pentanedione, (**88**) amines, (**6**) nitromethane (**89**) and aromatic aldehydes (**90**) in the presence of butylimidazolium tetrafluoroborate ([Hbim]BF_4) (**91**) afforded tetrasubstituted pyrroles (**92**) in good to excellent yields in short reaction times (**Scheme 3.24**). A variety of aromatic aldehydes and amines can be used, including alkynyl amines. The authors reported that only traces of the desired pyrroles were obtained when the reaction was carried out under neat conditions, and therefore it has to be assumed that the ionic liquid used as solvent has catalytic activity. The solvent can be reused up to three cycles without any appreciable loss of activity.[46]



Scheme 3.24 Four-component synthesis of pyrroles in an ionic liquid

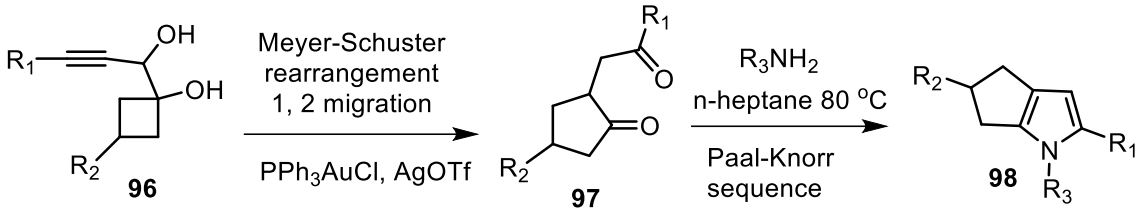
Recently Zhou *et al.* developed an organocatalyzed three-component reaction of 1, 2-diones, (**93**) aldehydes (**94**) and arylamines (**6**), which provides an efficient approach to access polysubstituted pyrroles (**95**) in acceptable to good yields under mild reaction conditions. The reaction involves the assembly of the pyrrole core from [1+1+3] atom fragments (**Scheme 3.25**).[47]



Scheme 3.25 Synthesis of polysubstituted pyrroles from aldehydes and primary amines

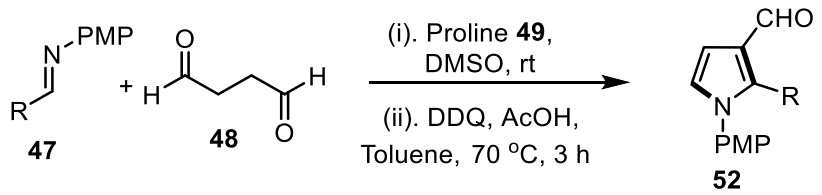
Recently Di Zhang and workers have reported gold catalyzed tandem reaction for the synthesis of 2-phenyl-1,4,5,6-tetrahydrocyclopenta[*b*]pyrrole derivatives (**98**) from 1-(1-hydroxy- 3-phenylprop-2-yn-1-yl)cyclobutanol (**96**) and primary amines (**6**) or NH_4OAc to afford a series of

polysubstituted pyrroles in moderate to good yields through intermediate (**97**) *via* 1, 2 migration of Meyer-Schuster rearrangement (**Scheme 3.26**).[48]



Scheme 3.26 Gold-catalyzed tandem synthesis of polysubstituted pyrrole

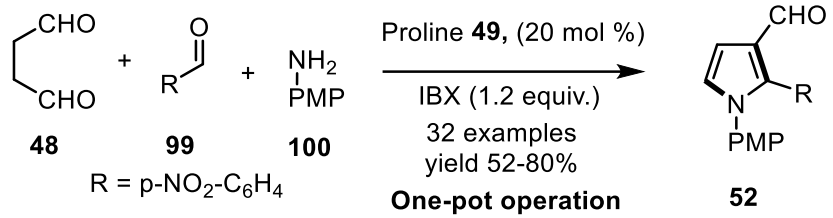
Recently Kumar and coworkers have reported the two pot synthesis of pyrrole-3-carboxaldehyde (**52**) *via* organocatalytic [3+2] direct Mannich cyclization cascade transformation followed by oxidative aromatization using DDQ as an oxidizing agent from succinaldehyde (**48**) and *N*-PMP aldimines (**47**) (**Scheme 3.27**).[49]



Scheme 3.27 Synthesis of pyrrole from succinaldehyde and imine

However, this method resulted in a quick synthesis of pyrrole ring moiety, but it required DDQ as harsh and toxic reagent for oxidative aromatization in two pot operation and also imine preparation separately which is time consuming. To overcome this limitation, herein we investigated modified organocatalytic approach towards the synthesis of functionalized 1, 2-diaryl-3-formylpyrrole (**52**) and related polycyclic natural product based scaffolds containing pyrrole core moiety by employing multicomponent one-pot tandem reaction sequences comprising an organocatalyzed [3+2] direct Mannich cyclization reaction followed by IBX triggered oxidative aromatization protocol from aromatic aldehydes (**99**) and *p*-anisidine (**100**) with a good combination of 1, 4-dicarbonyl compound such as succinaldehyde (**48**) which acts as 1, 3-carbon *donor-acceptor* (D-A) precursors in presence of proline (**49**) in DMSO **(Scheme 3.28**) to access direct synthesis of pyrroles having formyl functionality at C-3 position which is of the great interest in organic synthetic chemistry for further transformations towards the synthesis of various biologically active hybrid scaffolds. The reaction produced moderate to excellent yields (50–85%) of the corresponding substituted pyrroles within 8 to 24 hrs depending

on the substituents of the starting materials. IBX as a versatile and mild oxidizing agent makes this process greener, efficient, economic and environmentally benign process.



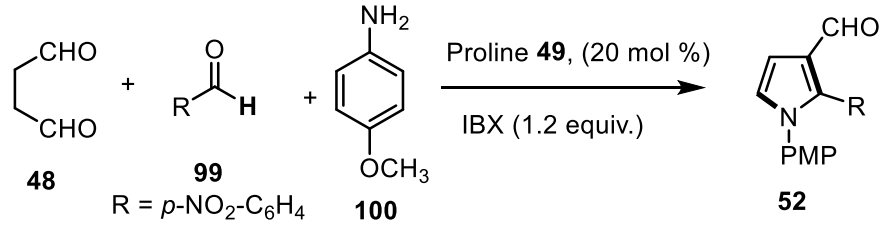
Scheme 3.28 Three-component pyrrole synthesis from succinaldehydean *in situ* imine

3.16 Results and discussion

We began our investigation while trying our initial experiment in DMSO using proline (**49**) as an amine catalyst, and obtained directly good yields in one-pot operation. In an effort to determine the appropriate reaction system, we carried out primary control experiments using aromatic aldehyde (**99**)**,** *p*-anisidine (**100**) and succinaldehyde (**48**) as representative model substrates. Keeping this idea in mind, we quickly established the reaction conditions for one-pot synthesis of 2, 3-disubstituted-3-formyl pyrroles (**52**) as shown in (**Table 3.3**). Our initial attempts give product (**52**) through *in situ* oxidation of enamine intermediate in DMSO at room temperature with less than 10% yields (**entries 1 and 2, Table 3.2**). Gratifyingly, *N*-PMP- 2, 3-disubstituted-3-formyl pyrroles (**52**) was obtained as the sole product with yields (upto 30-70%) when IBX (2-Iodoxybenzoic acid) was used as oxidizing agent at 40 °C to 70 °C in the same flask (**entry 3-5, Table 3.3**). In contrast this one-pot transformation was made feasible by taking advantage of IBX solubility in DMSO as well as enhancement in the yield upto (85%) and was observed as the most promising protocol when amino-catalyzed direct Mannich/cyclization sequence was carried out at room temperature followed by *in situ* IBX oxidation at 70 °C in one pot only without further extraction and purification for the synthesis of the desired product (**entry 6, Table 3.3**). Further increasing the reaction temperature during IBX oxidation (**entry 7, Table 3.3**) and catalyst loading (**entry 8, Table 3.3**) led to decrease in yields. Thus, we preferred to perform this one-pot, multicomponent sequence to *N*-PMP-2, 3-disubstituted-3-formylpyrroles (**52**) with optimized reaction condition (**entry 6, Table 3.3**). Further use of a solvent such as acetonitrile and DMF was not very successful with regard to yield of the reaction (**entry 9-11, Table 3.3**). Furthermore, varying the catalyst loading (**entry 8, Table 3.3**) and then using pyrrolidine (10 mol %) as a catalytic system (**entry 11, Table 3.3**) alters the reaction condition

with reduced yields, and also appropriate amount of IBX addition in the same pot at 70 ^{o}C is essential for enhancing the rate of aromatisation.

Table 3.3 Optimization of reaction conditions for the syntheses of **52b** using IBX

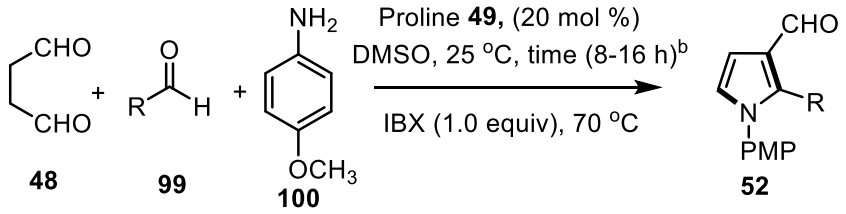


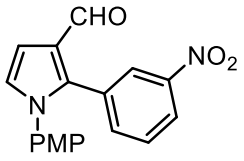
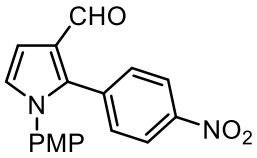
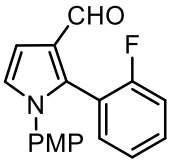
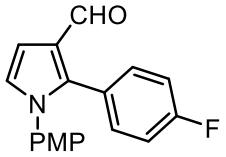
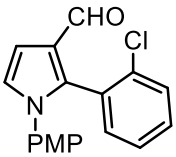
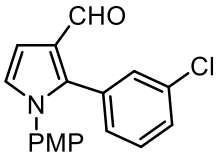
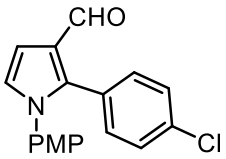
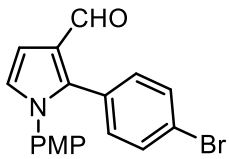
Entry	Conditions[a]		Yield[b] (%)
	Step 1	Step 2	
1	DMSO, rt, 8 h	IBX, rt, 12 h	<10
2	DMSO, rt, 8 h	IBX, rt, 24 h	<10
3	DMSO, rt, 8 h	IBX, 40 °C, 3 h	30
4	DMSO, rt, 8 h	IBX, 50 °C, 3 h	50
5	DMSO, rt, 8 h	IBX, 60 °C, 3 h	70
6	**DMSO, rt, 8 h**	**IBX, 70 °C, 3 h**	**85**
7	DMSO, rt, 8 h	IBX, 80 °C, 3 h	60
8[c]	DMSO, rt, 8 h	IBX, 70 °C, 3 h	58
9	DMF, rt, 8 h	IBX, 70 °C, 3 h	65
10	CH_3CN, rt, 8 h	IBX, 70 °C, 3 h	55
11[d]	DMSO, rt, 8 h	IBX,70 °C, 3 h	40

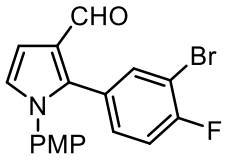
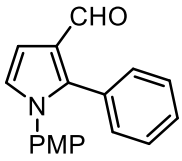
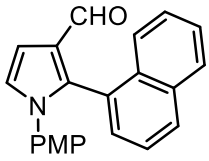
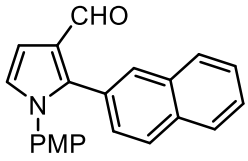
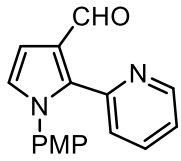
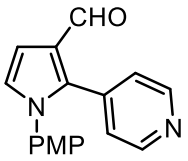
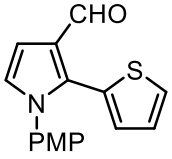
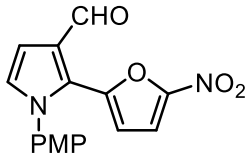
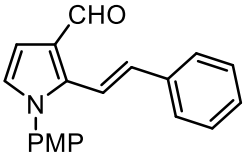
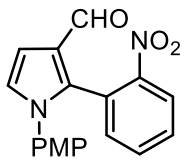
[a]Unless otherwise indicated, the reaction was carried out with (i) aldehyde **99**(0.3 mmol), *p*-anisidine **100** (0.3 mmol), **48** (3M aqueous sol., 0.9 mmol), L-proline **49** (20 mol %), solvent (3.0 mL); (ii) oxidant IBX (100 mol %). [b]Isolated yield of **52** refers to **99**. [c]Catalyst **49** (10 mol %). [d]Pyrrolidine (20 mol %), were used in place of **49.**

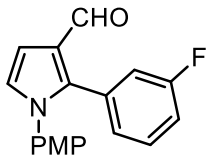
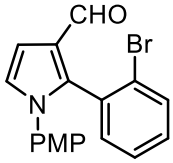
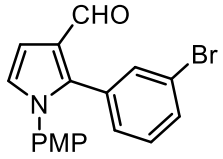
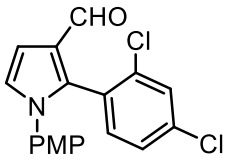
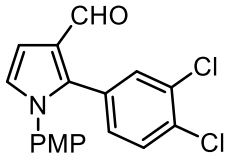
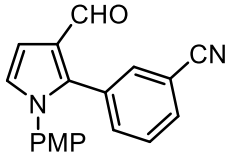
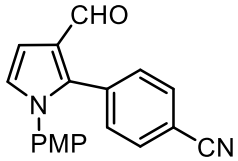
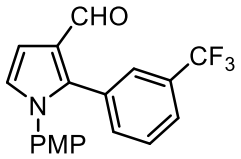
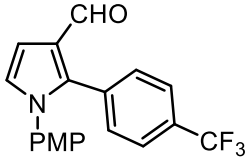
With the optimal conditions in hand, we next examined the generality of this developed transformation by employing various electron deficient aromatic aldehydes and *p*-anisidine and the results are summarized in (**Table 3.4**). The reaction proceeded with high yields in case of electron-deficient aryl-aldehydes (**entry 1-12, 18, and 19-27,Table 3.4**). However, in cases of

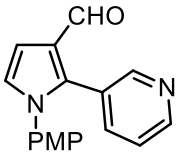
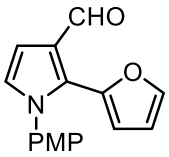
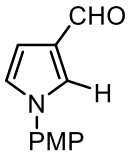
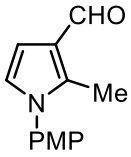
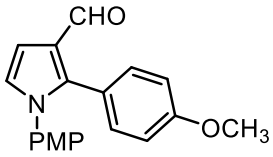
Table 3.4 Synthesis of substituted pyrroles from various aldehydes[a]



Entry	R	Product	52	% Yield[b]
1	3-NO_2-C_6H_4		**52a**	78
2	4-NO_2-C_6H_4		**52b**	82
3	2-F-C_6H_4		**52c**	71
4	4-F-C_6H_4		**52d**	76
5	2-Cl-C_6H_4		**52e**	69
6	3-Cl-C_6H_4		**52f**	74
7	4-Cl-C_6H_4		**52g**	77
8	4-Br-C_6H_4		**52h**	73

Entry	R	Product	52	% Yield[b]
9	3-Br,4-F-C_6H_3		**52i**	69
10	C_6H_5		**52j**	65
11	1-napthyl		**52k**	61
12	2-napthyl		**52l**	63
13	2-pyridyl		**52m**	72
14	4-pyridyl		**52n**	74
15	2-thienyl		**52o**	68
16	5-NO_2,2-furyl		**52p**	74
17	(E)CH=CHC_6H_5		**52q**	60
18	2-NO_2-C_6H_4		**52r**	67

Entry	R	Product	52	% Yield[b]
19	3-F-C_6H_4		**52s**	69
20	2-Br-C_6H_4		**52t**	62
21	3-Br-C_6H_4		**52u**	68
22	2-Cl,4-Cl-C_6H_3		**52v**	63
23	3-Cl,4-Cl-C_6H_3		**52w**	59
24	3-CN-C_6H_4		**52x**	62
25	4-CN-C_6H_4		**52y**	68
26	2-CF_3-C_6H_4		**52z**	53
27	4-CF_3-C_6H_4		**52aa**	64

Entry	R	Product	**52**	% Yield[b]
28	3-pyridyl		**52ab**	66
29	2-furyl		**52ac**	57
30	H		**52ad**	50
31	Me		**52ae**	n.r
32	4-OCH_3-C_6H_4		**52af**	n.r

[a](i) aldehyde **99** (0.3 mmol), *p*-anisidine **100** (0.3 mmol), **48** (3M sol, 0.9 mmol), **49** (20 mol %), DMSO (3.0 mL), [b]Isolated yields refer to **99**

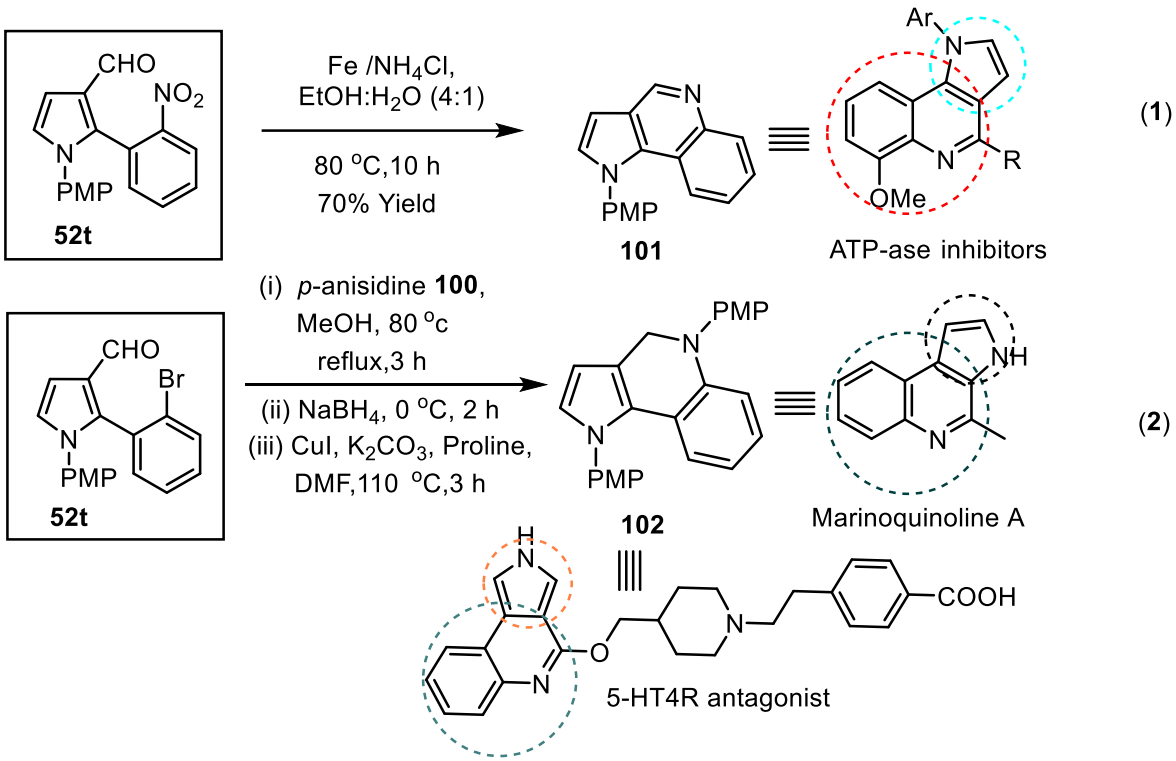
ortho-substituted benzaldehydes (**entry 3, 5, 18, 20 and 26, Table 3.4**) and disubstituted chloro-benzaldehydes and napthaldehydes (**entry 11, 12, 22 and 23, Table 3.4**), reactions were rather slow with lower yields, perhaps owing to steric crowding. Not only aryl aldehydes but hetero-aryl aldehydes too resulted in products with high yields (**entry 13-16, and 28-29, Table 3.4**), while the reactions with an alkenyl aldehyde (**entry 17, Table 3.4**) works significantly and reactions with *in situ* generated imine from formaldehyde (**entry 30, Table 3.4**) were sluggish, resulting products in low yields. This reaction is limited to electron deficient aldehydes as the reaction failed in the case of electronically rich aryl as well as in aliphatic aldehydes (**entry 31-32, Table 3.4**).

The desired compound pyrrole-3-carboxaldehdyes (**52**) was isolated by column chromatography and their structures were characterized by ^{1}H NMR, ^{13}C NMR, IR, single X-ray difraction and

HRMS mass data. A representative ^{1}H and ^{13}C NMR of **(52r)** is shown in (**Figure 3.5**).

The present one pot protocol resulting pyrrole (**52**) having the C-3 formyl functionality are important synthetic intermediates for further functionalization in organic synthesis.

A reduction reaction of (**52r**) provided the corresponding pyrroloquinoline core containing natural product (**101**) in just one step, which is not possible by any other process.[50] In this reaction reduction of nitro compound takes place in the presence of Fe/NH_4Cl in EtOH:H_2O (4:1) followed by *in situ* imine formation producing corresponding pyrroloquinoline compound (**101**) with good yields (**Eqn 1, Scheme 3.29**).

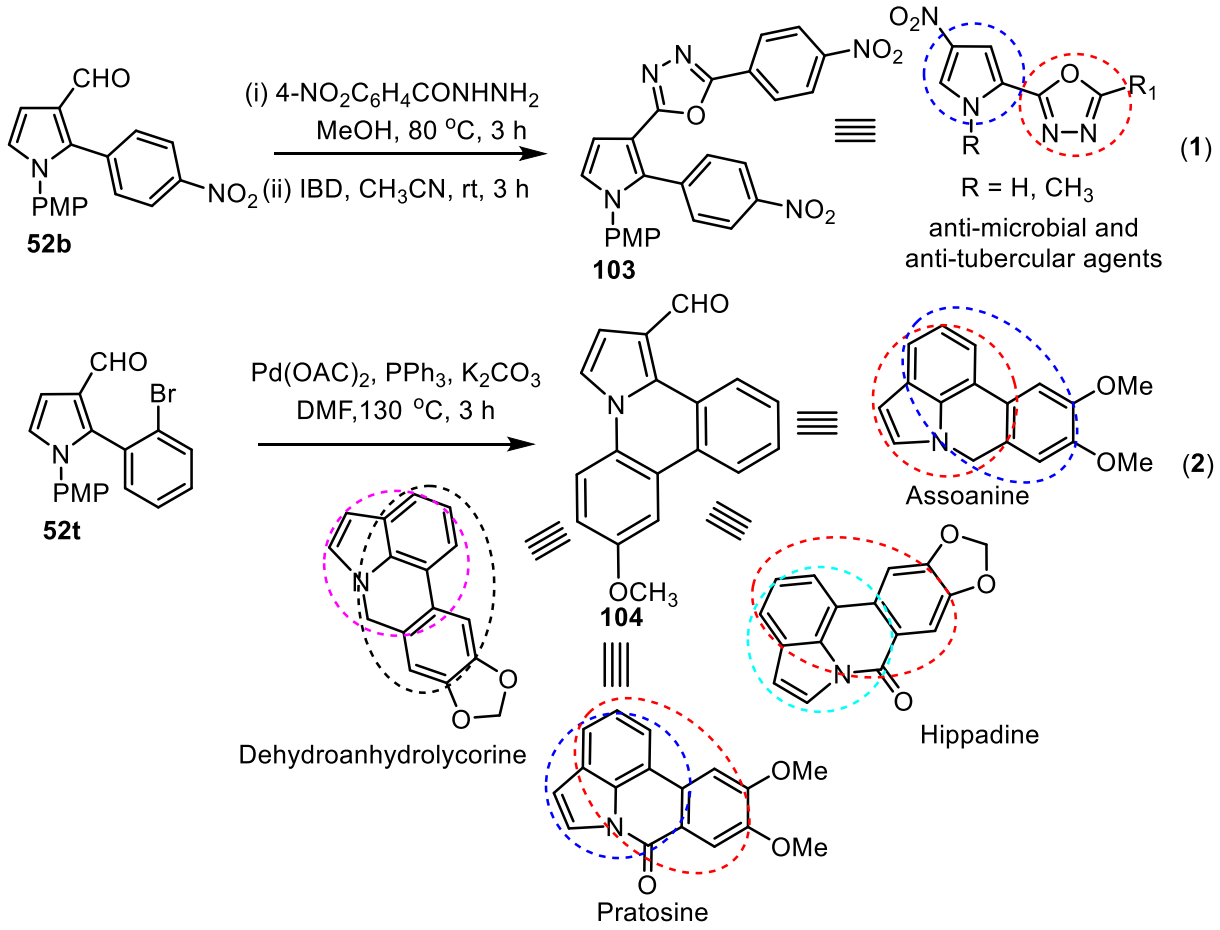


Scheme 3.29 Synthesis of pyrroloquinoline based hybrid scaffold

For the synthesis of pyrrolo-dihydroquinoline (**102**), we firstly condense (**52t**) with *p*-anisidine (**100**) followed by the reductive amination in the same pot and hence finally coupled the resulting intermediate product with copper iodide (CuI), base (K_2CO_3) and proline as a ligand as shown in (**Eqn 2, Scheme 3.29**).[51] These synthesized hybrid scaffolds resemble with various biologically active molecules such as pyrrolo-[3,2-c]quinoline derivative, an ATP-ase inhibitor,[52] pyrrolo-[2,3-c]quinoline derivative, a natural product with acetylcholinesterase-inhibiting activity[53] and pyrrolo-[3,4-c] quinoline derivative, a potent 5-HT4R antagonist with analgesic action.[54]

In another application, compound pyrrolo-oxadiazole fused hybrid product (**103**) was successfully prepared through the expected condensation of *p*-nitrophenylhydrazide and starting material (**52b)** followed by IBD oxidation in the same vessel (**Eqn 1, Scheme 3.30**).[55]

In addition Palladium-catalyzed C-C bond formation in the presence of $Pd(OAc)_2$, triphenylphosphine as ligand and base (K_2CO_3) in DMF yielding hybrid product pyrrole-phenanthridine scaffold (**96)** from (**52t)** (**Eqn 2, Scheme 3.30**).[56] These synthesized pyrrolo-phenanthridine moieties have a close resemblance with assoanine natural product which was originally isolated from *Narcissus pseudo narcissus* by Wildman *et al*. in 1956, is representative of this class of alkaloids,[57] including pratosine,[58] hippadine,[59] and dihydroanhydrolycorin,[60] isolated from plants belonging to the Amaryllidaceae species. Pyrrolo-phenanthridine alkaloids have been reported to exhibit various biological properties and have consequently received considerable attention from both chemists and biological scientists.



Scheme 3.30 Synthesis of pyrrole-oxadiazole, and pyrrole-phenanthridine moieties

3.17 Conclusions

In summary, we have developed a flexible and general solution for the synthesis of various functionalized disubstituted-3-formyl pyrroles via an organocatalyzed [3+2] annulation of various aromatic aldehydes (**99**), *p*-anisidine (**100**) and succinaldehyde (**48**) through direct Mannich multi-component reaction transformation followed by IBX triggered oxidative aromatization sequence in one pot operation. The use of readily available substrates, a simple procedure, and mild reaction conditions and, in particular, no need to exclude moisture or air renders this method potentially useful in organic synthesis. The synthetic usefulness of this method lies in the fact that *in situ* imines generated from aromatic aldehydes(**99**) and *p*-anisidine (**100**) were efficiently functionalized to access pyrrole-3-carbaldehyde derivatives (**52**) with further applications towards the synthesis of substituted pyrroloquinoline (**101**)**,** dihydro-pyrroloquinoline (**102**), pyrrole-oxadiazole (**103**) and pyrrole- phenanthridine (**104**) moieties in just one step which are analogous to various natural products having infinite applications in biology and medical sciences.

3.18 General Experimental Methods

All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on SiO_2 gel F-254 plates. Unless otherwise noted all reactions have been carried out with distilled and dried solvents. Oven (120 °C) dried glasswares were used. All work up and purification were carried out with reagent grade solvents in the air. The normal column chromatography was performed on silica gel (100-200 mesh) and Flash column chromatography was performed on silica gel (230-400 mesh) 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 on a BRUKER-AV400 (400 MHz and 75 MHz) spectrometer 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. Infrared (FT-IR) spectra were recorded on an ABB Bomen MB 3000 FTIR Spectrophotometer system using KBr pellets.

3.19 Representative procedure for the synthesis of pyrrole-3-carboxaldehydes (52) in one-pot sequential approach

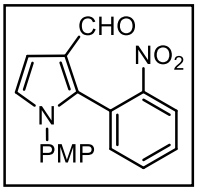
Succinaldehyde (**48**) (0.3 mL, 0.9 mmol, 3M solution) was added to a mixture of *in situ N*-PMP aldimine from aldehyde (**99**) (0.3 mmol)**,** *p*-anisidine (**100**) (0.3 mmol)**,** and L-proline (**49**) (7.0

mg, 0.06 mmol) in DMSO (3.0 mL) at room temperature. The reaction mixture was stirred at room temperature until the aldimine was consumed as monitored by TLC. Further, in the same pot IBX (84 mg, 0.3 mmol, 1.0 equiv.) was added and the reaction mixture was stirred and heated at 70 ^{o}C for 3 h and cooled to room temperature. The reaction was quenched with a saturated $NaHCO_3$ solution (3 mL) and extracted with ethyl acetate (6 mL) with three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification through silica gel column chromatography by eluting the mixture of EtOAc/ hexane gave pyrrole 3-carbxaldehydes (**52**) with high yields (50-82%). The pure products were characterized based upon their spectroscopic data.

3.20 Analytical data of synthesized compounds (52a-52q) are mentioned in Chapter III A.

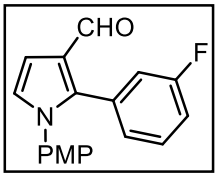
Additional data of synthesized compounds (52r-52ad) are summarized as given below:

1-(4-methoxyphenyl)-2-(2-nitrophenyl)-1H-pyrrole-3-carbaldehyde (52r)



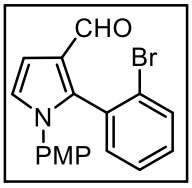
Yield (64 mg, 67%, pasty red); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 3.0 Hz, 1H), 7.02 (d, *J*= 8.9 Hz, 2H), 7.45 (d, *J* = 6.5 Hz, 1H),7.54 (t, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 6.6 Hz, 1H), 7.97 (d, *J* = 8.1 Hz, 1H), 9.60 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.42, 109.16, 114.37 (2C), 124.45, 124.80, 125.18, 125.20, 126.94 (2C), 130.09, 130.81, 132.78, 134.17, 135.84, 149.37, 159.10, 185.54; IR (KBr)/cm^{-1} 2932, 1666, 1520, 1350, 1296, 1034; HRMS (ESI): Calcd for $C_{18}H_{14}N_2O_4$ (MH^+) 323.1033; Found 323.1013.

2-(3-fluorophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (52s)



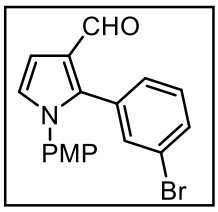
Yield (62 mg, 69%, pasty yellow liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 6.83 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 3.1 Hz, 1H), 6.89 (d, *J* = 2.8 Hz, 1H), 6.91 (t, J=1.8 Hz, 1H), 7.00-7.06 (m, 4H), 7.28-7.32 (m,1H),9.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.45, 107.88, 114.37 (2C), 115.71, 117.92, 124.64, 125.27, 126.81, 127.02, (2C), 129.83, 129.90, 131.36, 140.49, 158.96, 161.22, 186.69; IR (KBr)/cm^{-1} 2962, 1720, 1512, 1247,1172; HRMS (ESI): Calcd for $C_{18}H_{14}FNO_2$ (MH^+) 296.1087; Found 296.1070.

2-(2-bromophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (52t)



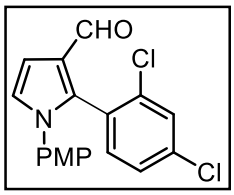
Yield (66 mg, 62%, red viscous liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.86 (d, *J* = 3.1 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.9 Hz, 2H), 7.39-7.45 (m, 3H), 7.57 (d, J= 7.9 Hz, 2H), 9.51 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.40, 107.53, 114.84 (2C), 122.27, 122.80 (2C), 124.56, 126.68 (2C),126.89, 128.60, 130.69, 132.91, 133.24, 133.52, 158.88, 186.28; IR (KBr)/cm^{-1} 3016, 1720, 1519, 1226, 1026; HRMS (ESI): Calcd for $C_{18}H_{14}BrNO_2$ (MH^+) 356.0286; Found 356.0295.

2-(3-bromophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (52u)



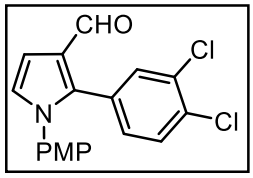
Yield (73 mg, 68%, brown pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.84 (d, *J* = 2.1 Hz, 1H), 6.86 (d, *J* = 4.1 Hz, 2H), 6.89 (d, *J* = 3.0 Hz, 1H), 7.03 (d, J= 7.0 Hz, 2H), 7.08-7.11 (m, 1H), 7.17 (t, J= 7.8 Hz, 1H) 7.41 (t, J= 1.7 Hz, 1H) 7.45-7.48 (m, 1H), 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.50, 108.03, 114.46 (2C), 122.26, 122.82, 124.78, 125.32 ,127.13 (2C), 129.50, 129.70, 131.38, 131.61, 133.76, 137.29, 159.08, 186.58; IR (KBr)/cm^{-1} 2985, 1728, 1519, 1373, 1242,1049; HRMS (ESI): Calcd for $C_{18}H_{14}BrNO_2$ (MH^+) 356.0286; Found 356.0295.

2-(2,4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (52v)



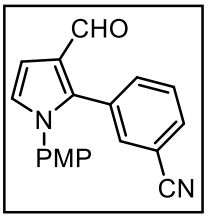
Yield (66 mg, 63%, yellow oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.80 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 3.1 Hz, 1H), 6.94 (d, *J* = 2.9 Hz, 1H), 7.03 (d, *J* = 8.9 Hz, 2H), 7.24 (d, *J* = 1.7 Hz, 2H),7.40 (s, 1H), 9.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.42, 107.99, 114.26 (2C), 124.99, 125.16, 126.53 (2C),126.99, 127.70, 129.73, 131.32, 134.05, 135.96, 136.11, 137.27, 158.96, 185.95; IR (KBr)/cm^{-1} 2954, 1668, 1514, 1469, 1246, 1031; (ESI): Calcd for $C_{18}H_{13}Cl_2NO_2$ (MH^+) 368.0221; Found 368.0226.

2-(3, 4-dichlorophenyl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (52w)



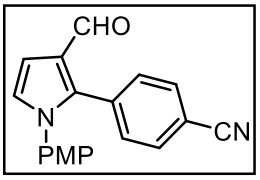
Yield (63 mg, 59%, yellow pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 6.74 (d, *J* = 3.7 Hz, 2H), 6.75 (s, 1H), 6.78 (d, *J* = 3.1 Hz, 1H), 6.86-6.92 (m, 3H), 7.14 (s, 1H), 7.23 (t, *J* = 2.2 Hz, 2.0 Hz, 1H), 9.58 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.49, 108.29, 114.52 (2C), 124.76, 125.52, 127.11(2C), 129.30, 129.94, 130.27, 131.05, 132.51,132.58, 133.02, 138.85, 159.12, 186.24; IR (KBr)/cm^{-1} 2962, 1697, 1514, 1253, 1031; (ESI): Calcd for $C_{18}H_{13}Cl_2NO_2$ (MH^+) 368.0221; Found 368.0226.

3-(3-formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl) benzonitrile (52x)



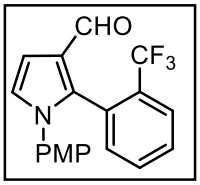
Yield (57 mg, 62%, yellow pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.84 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 7.01 (d,*J* = 8.9 Hz, 2H), 7.42-7.49 (m, 3H), 7.41 (d, *J*= 7.0 Hz, 1H) 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.48, 108.65, 112.69, 114.60 (2C), 118.02, 124.89, 125.70, 127.14 (2C), 129.18, 130.87, 130.93, 131.92, 134.02, 135.11, 138.47, 159.23, 186.02; IR (KBr)/cm^{-1} 2932, 2230, 1659, 1512, 1443, 1250; HRMS (ESI): Calcd for $C_{19}H_{14}N_2O_2$ (MH^+) 303.1134; Found 303.1134.

4-(3-formyl-1-(4-methoxyphenyl)-1H-pyrrol-2-yl) benzonitrile (52y)



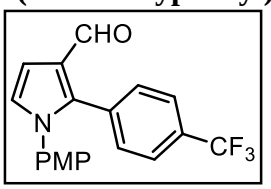
Yield (62 mg, 68%, pinkish pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 8.3 Hz, 2H), 9.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.52, 108.93 (2C), 114.51,114.63 (2C),114.95,118.25, 122.86, 124.95, 125.05, 125.96, 127.15 (2C), 129.24, 130.26, 131.10, 131.44 (2C), 131.95 (2C),132.16, 134.15, 134.60, 138.26, 141.82, 159.31, 186.09; IR (KBr)/cm^{-1}2933, 1724, 1660, 1249, 1174; IR (KBr)/cm^{-1} 2962, 2229, 1712, 1519, 1242; HRMS (ESI): Calcd for $C_{19}H_{14}N_2O_2$ (MH^+) 303.1134; Found 303.1134.

1-(4-methoxyphenyl)-2-(2-(trifluoromethyl)phenyl)-1H-pyrrole-3-carbaldehyde (52z)



Yield (57 mg, 53%, yellow pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 3.1 Hz, 1H), 6.91 (d, *J* = 3.0 Hz, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.37 (t, *J* = 4.5 Hz, 1H), 7.51 (t, *J* = 4.9 Hz, 2H), 7.70 (t, *J* = 4.6 Hz, 1H), 9.41 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.39, 107.55, 114.11 (2C), 114.60, 117.68, 120.11, 121.55, 122.04, 124.88, 126.55, 127.01 (2C), 129.54, 131.13, 131.43, 134.09, 158.92, 186.02; IR (KBr)/cm^{-1} 2955, 1666, 1520, 1311, 1250, 1119; (ESI): Calcd for $C_{19}H_{14}F_3NO_2$ (MH^+) 368.0875; Found 368.0881.

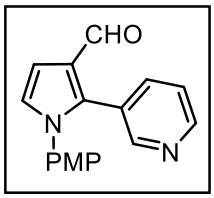
1-(4-methoxyphenyl)-2-(4-(trifluoromethyl)phenyl)-1H-pyrrole-3-carbaldehyde (52aa)



Yield (68 mg, 64%, yellow pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.84 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 3.1 Hz, 1H), 6.92 (d, *J* = 3.0 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.58 (d, *J* = 8.1 Hz, 2H), 9.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.48, 108.39 (2C), 114.52 (2C), 124.94 , 125.17, 125.21, 125.24, 125.28, 125.61(2C), 127.14 (2C), 131.19 (2C),131.28, 159.12,

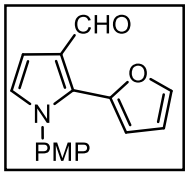
186.41; IR (KBr)/cm^{-1} 2970, 1666, 1512, 1319, 1234; (ESI): Calcd for $C_{19}H_{14}F_3NO_2$ (MH^+) 368.0875; Found 368.0881.

1-(4-methoxyphenyl)-2-(pyridin-3-yl)-1H-pyrrole-3-carbaldehyde (52ab)



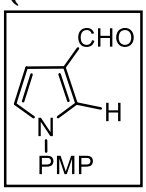
Yield (55 mg, 66%, red oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 3.0 Hz, 1H), 6.96 (d, *J* = 2.9 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 2H), 7.28 (t, *J* = 3.7 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 8.5 (bs, 1H), 8.58 (d, J= 4.7 Hz, 1H), 9.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.46, 108.48, 114.56 (2C),122.98, 125.14, 125.71, 125.75, 127.31 (2C), 131.04, 137.86, 137.98, 149.40, 151.04, 159.21, 186.09; IR (KBr)/cm^{-1} 2954, 1666, 1512, 1242, 1033; HRMS (ESI): Calcd for $C_{17}H_{14}N_2O_2$ (MH^+) 279.1133; Found 279.1140.

2-(furan-2-yl)-1-(4-methoxyphenyl)-1H-pyrrole-3-carbaldehyde (52ac)



Yield (45 mg, 57%, red oily liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.05 (d, *J* = 3.3 Hz, 1H), 6.37 (d, *J* = 3.2 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 7.18 (d, *J* = 8.8 Hz, 3H), 7.99 (d, *J* = 7.7 Hz, 1H),8.05 (d, *J* = 7.9 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.51, 108.14, 111.20, 111.76, 114.38 (2C), 126.01, 127.24 (2C), 127.94, 131.84, 133.19, 141.73, 143.44, 159.44, 187.40; IR (KBr)/cm^{-1} 2970, 1682, 1582, 1466, 1265, 1011; HRMS (ESI): Calcd for $C_{16}H_{13}NO_3$ (MH^+) 268.0974; Found 268.0980.

1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (52ad)

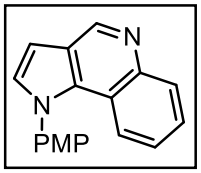


Yield (30 mg, 50%, yellow pasty liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.86 (s, 3H), 6.78 (s, 1H), 6.99 (d, *J* = 9.0 Hz, 3H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.58 (s, 1H), 9.84 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.62, 109.35, 114.92 (2C), 122.73, 122.79 (2C), 127.39, 127.83, 133.08, 158.87, 186.49; IR (KBr)/cm^{-1} 2916, 1668, 1519, 1274, 1247, 1176; HRMS (ESI): Calcd for $C_{12}H_{11}NO_2$ (MH^+) 202.0869; Found 202.0873.

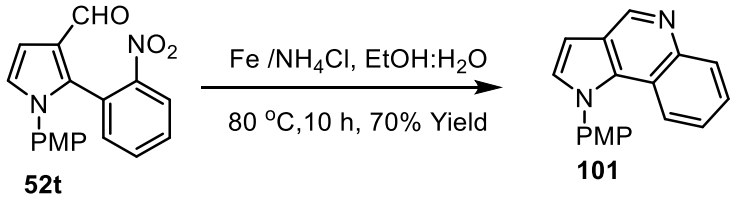
3.21 General procedure for the synthesis of 1-(4-methoxyphenyl)-1H-pyrrolo [3,2-*c*] quinoline (101)

To a mixture of compound (**52r**) (50 mg, 0.15 mmol), Fe powder (86.9 mg, 1.55 mmol, 10.0 equiv.) and NH_4Cl (100 mg, 1.8 mmol, 12.0 equiv.) in EtOH:H_2O (5 mL, 4:1) was heated at 80 ^oC for 10 h. Afterwards the reaction mixture was concentrated under reduced pressure. The crude residue was extracted with ethyl acetate. The combined organic solvent evaporated under reduced pressure and followed by purification through a pad of silica-gel (eluent: hexane/ethyl

acetate = 3:1) afforded the pure product (**101)** as pasty yellow liquid (28 mg, 67% yield) (**Scheme 3.31)**.



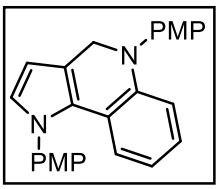
^{1}H NMR (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 6.87 (d, *J* = 3.1 Hz, 1H), 7.09 (d, *J* = 8.6 Hz, 2H), 7.21 (d, *J* = 3.1 Hz, 1H), 7.23 (t, *J* = 1.1 Hz, 1H), 7.38 (d, *J* = 9.1 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.53 (t, *J* = 7.0 Hz, 1H), 8.19 (d, *J* = 8.3 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.65, 103.37, 114.83 (2C), 118.25, 120.60, 121.65, 125.35, 126.44, 128.54 (2C), 129.97, 130.27, 133.29, 134.66, 144.20, 146.16, 159.96; IR (KBr)/cm^{-1} 2924, 1713, 1512, 1366, 1250, 1034; HRMS (ESI): Calcd for $C_{18}H_{14}N_2O$ (MH^+) 275.1185; Found 275.1190.



Scheme 3.31 Synthesis of pyrroloquinoline based hybrid scaffold

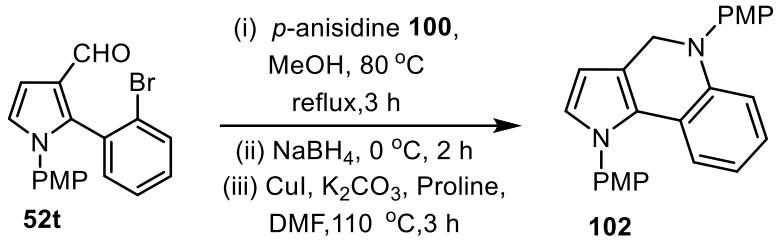
3.22 Experimental procedure for the synthesis of 1,5-bis(4-methoxyphenyl)-4,5-dihydro-1H-pyrrolo-[3,2 *c*]quinoline (102)

A mixture of (**52t**) (0.1g, 0.28 mmol, 1.0 equiv) and *p*-anisidine (0.030g, 0.28 mmol, 1.0 equiv) in methanol (3 mL) was refluxed for 2 hrs at 80 °C followed by reductive amination in the presence of $NaBH_4$ at 0 °C to obtain intermediate product for further coupling reaction. Then for the next step, this intermediate (0.1g, 0.22 mmol, 1.0 equiv) was taken in oven-dried round-bottom flask dissolved in DMF (2 mL), followed by the addition of base K_2CO_3 (61 mg, 0.44 mmol, 2.0 equiv.), CuI (9 mg, 20 mol %), L-proline as ligand (10 mg, 40 mol %).The resulting solution was stirred at 110°C for 3 h under an N_2 atmosphere. On completion, the residue was cooled to ambient temperature and then diluted with water (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc/hexanes) to afford (**102**) as yellow pasty liquid (70 mg, 87% yield) (**Scheme 3.32**).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.56 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.28 – 7.33 (m, 1H), 7.23 (d, *J* = 9.0 Hz, 2H), 7.08 – 7.14 (m, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.74 (d, *J* = 1.8 Hz, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.47 (d, *J* = 8.9 Hz, 2H), 6.25 (dd, *J* = 2.8,

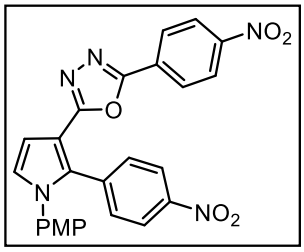
1.8 Hz, 1H), 5.80 (s, 1H), 3.81 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.62, 151.97, 142.23, 141.30, 134.14, 132.93, 128.44, 128.15, 127.80, 126.79, 123.57, 121.93 (2C), 119.96, 118.18, 114.77 (2C), 114.55 (2C), 114.25 (2C), 109.20, 56.26, 55.70, 55.52; HRMS (ESI): Calcd for $C_{25}H_{22}N_2O_2$ (MH^+) 383.1759; Found 383.1765.



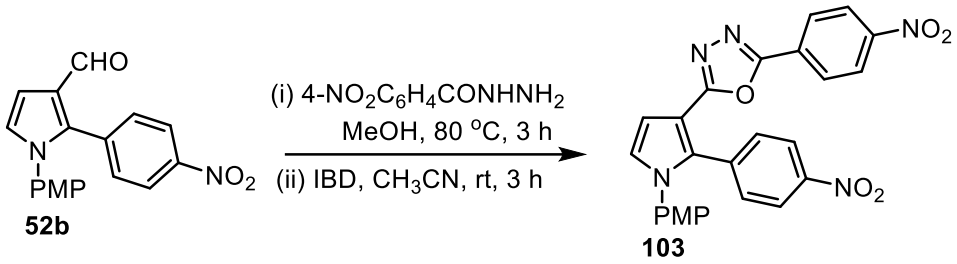
Scheme 3.32 Synthesis of dihydropyrroloquinoline based hybrid scaffold

3.23 Experimental procedure for the synthesis of 2-(1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrol-3-yl)-5-(4-nitrophenyl)-1,3,4 oxadiazole (103)

A mixture of (**52b**) (0.08g, 0.24 mmol, 1.0 equiv) and 4-nitrobenzohydrazide (0.044g, 0.24 mmol, 1.0 equiv) in methanol (3 mL) was stirred for 2 hours under 80°C and then concentrated under vacuum. Then followed by the addition of IBD (0.08g, 0.24 mmol, 1.0 equiv) dissolved in acetonitrile (3mL) in the reaction vessel and stirred at room temperature for one hour. The mixture was then concentrated under vacuum. To the residue was added H_2O (10mL) and the resulting mixture was extracted with ethylacetate (10 mLX3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using (eluent: hexane/ethyl acetate = 2:1) affording final product (**103**) as yellow foamy solid (92 mg, 76% yield) (**Scheme 3.33**).



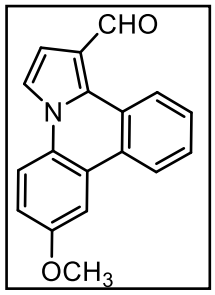
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 9.0 Hz, 2H), 8.17 (d, *J* = 8.9 Hz, 2H), 8.08 (d, *J* = 9.0 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 3.0 Hz, 1H), 7.04 (d, *J* = 9.0 Hz, 2H), 7.01 (d, *J* = 3.0 Hz, 1H), 6.84 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.72, 161.69, 159.21, 149.25, 147.31, 137.09, 132.45, 132.05 (2C), 131.37, 129.44, 127.33 (2C), 127.18 (2C) 125.92, 124.38 (2C), 123.07 (2C), 114.57 (2C), 109.88, 108.01, 55.50; HRMS (ESI): Calcd for $C_{25}H_{17}N_5O_6$ (MH^+) 484.1258; Found 484.1263.



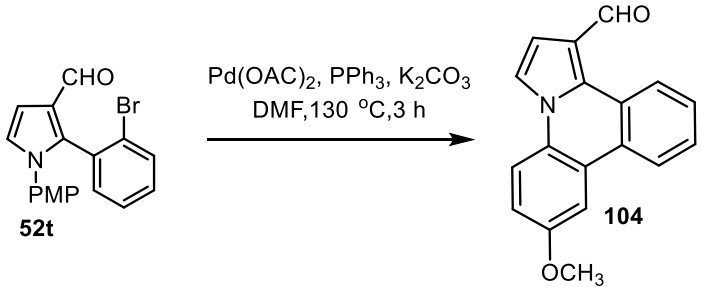
Scheme 3.33 Synthesis of pyrrolo-oxadiazole based hybrid scaffold

3.24 General procedure for the synthesis of 7-methoxypyrrolo-[1, 2-*f*]phenanthridine-1-carbaldehyde (104)

A clean oven-dried 10 mL round-bottom flask was charged with **(52t)** (70 mg, 0.19 mmol, 1.0 equiv.), K_2CO_3 (54 mg, 0.39 mmol, 2.0 equiv.), ligand PPh_3 (10 mg, 20 mol %), Pd $(OAc)_2$ (5 mg, 10 mol %), and DMF (2 mL). The resulting solution was stirred at 130 °C for 3 h under an N_2 atmosphere. On completion, the reaction mass was cooled to ambient temperature and then diluted with water (5 mL) and extracted with EtOAc (2 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated to dryness. The crude residue so obtained was purified by column chromatography (EtOAc/hexanes) to afford (**104**) as white foamy solid (43 mg, 78% yield) (**Scheme 3.34)**.



^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 9.49 (dd, *J* = 7.1, 2.3 Hz, 1H), 8.33 (dd, *J* = 7.3, 2.2 Hz, 1H), 7.88 (d, *J* = 9.2 Hz, 1H), 7.85 (d, *J* = 2.7 Hz, 1H), 7.80 (d, *J* = 3.3 Hz, 1H), 7.62 – 7.70 (m, 2H), 7.24 (d, *J* = 3.3 Hz, 1H), 7.22 (dd, *J* = 9.1, 2.8 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 185.15, 157.25, 128.72, 128.59, 127.40, 127.20, 125.37, 123.96, 122.27, 120.55, 119.08, 117.77, 117.20, 117.04, 115.10, 114.06, 106.68, 55.72; HRMS (ESI): Calcd for $C_{18}H_{13}BrNO_2$ (MH^+) 276.1024; Found 276.1029.



Scheme 3.34 Synthesis of pyrrolo-phenanthridine based hybrid scaffold

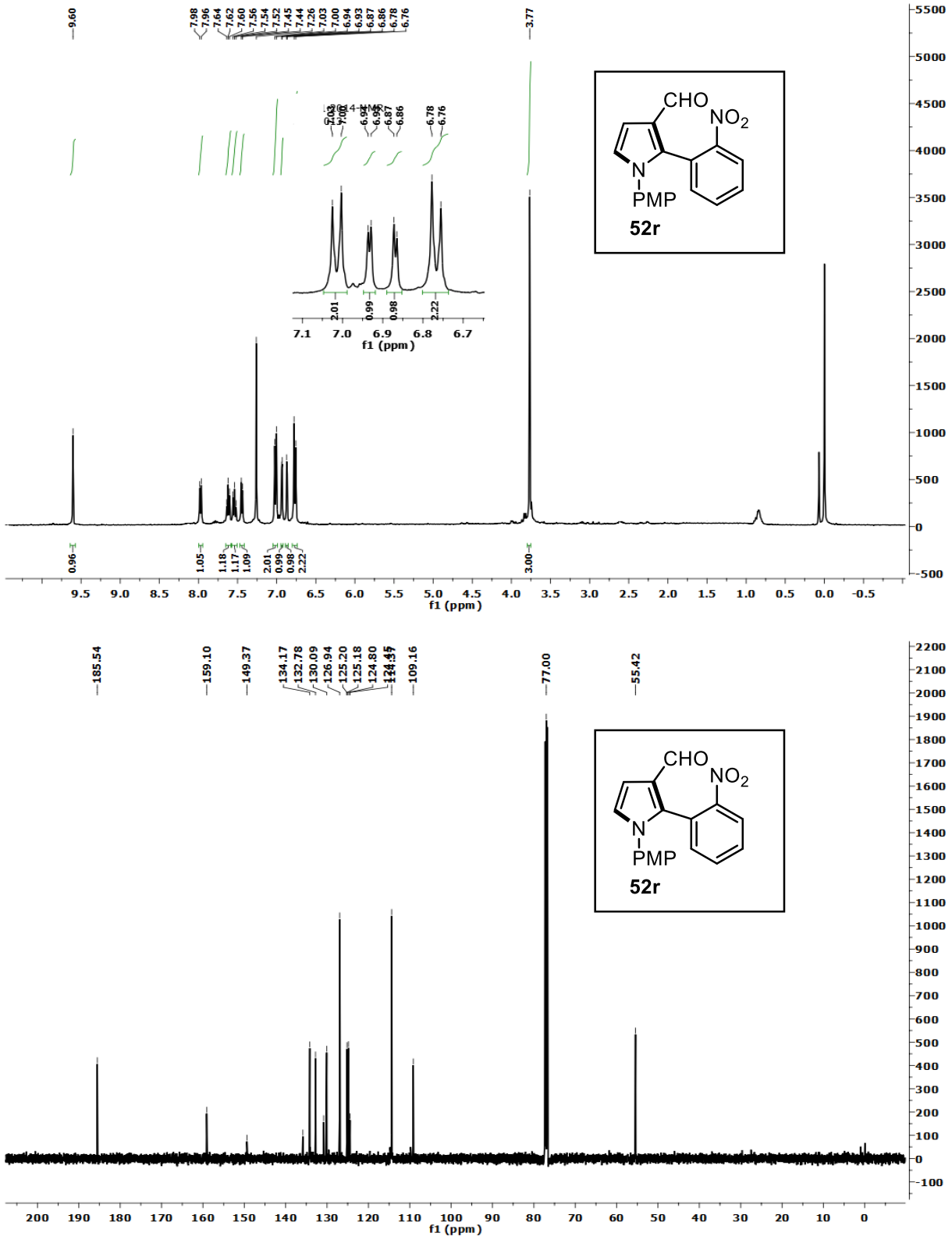


Figure 3.5 ^{1}H and ^{13}C NMR spectra of 1-(4-methoxyphenyl)-2-(2-nitrophenyl)-1H-pyrrole-3-carbaldehyde (**52r**)

3.25 Crystal data analysis of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrole-3-carbaldehyde (52b) with [CCDC No. 1400572]

Table 3.5 Crystal data for **52b**

CCDC	**1400572**
Crystal description	white block
Crystal size	0.3 X 0.2 X 0.2 mm
Empirical formula	$C_{18}H_{14}N_2O_4$
Formula weight	322.31
Radiation, Wavelength	Mo *Kα*, 0.71073 Å
Unit cell dimensions	a= 8.0230(6), b= 10.5211(8),
c= 18.4479(16) Å	
Crystal system	orthorhombic
Space group	$P2_12_12_1$
Unit cell volume	1557.2(2)
No. of molecules per unit cell, Z	4
Temperature	293(2) K
Absorption coefficient	0.099 mm^{-1}
F(000)	672
Scan mode	ω scan
θ range for entire data collection	$3.84 < \theta < 26.00$
Range of indices	h= -8 to 9, k= -5 to 12, l= -13 to 22
Reflections collected / unique	4243/ 1762
Reflections observed ($I > 2\sigma(I)$)	1184
R_{int}	0.0390
R_{sigma}	0.0639
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	218
Final R	0.0511
$wR(F^2)$	0.0913
Weight	$1/[\sigma^2(F_o^2)+(0.0412P)^2+0.0000P]$
Where $P=[F_o^2+2F_c^2]/3$	
Goodness-of-fit	1.032
Final residual electron density	$-0.194 < \Delta\rho < 0.143 eÅ^{-3}$

The compound (**52b**) crystallizes in the orthorhombic space group $P2_12_12_1$ with the unit-cell parameters: a= 8.0230(6), b= 10.5211(8), c= 18.4479(16) 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 0.0511 for 1184 observed reflections. X-ray intensity data of 4243 reflections (of which 1762 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 1096 reflections in the θ range 3.85 to 25.01°**.** The intensities were measured by ώ scan mode for θ ranges 3.84 to26.00°. 1184 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz, polarisation 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 = 0.0511 and wR (F^2) = 0.0913 for the observed data. Residual electron densities ranged from $-0.194 < \Delta\rho < 0.143 eÅ^{-3}$. 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 3.5**). An ORTEP view of the molecule 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1H-pyrrole-3-carbaldehyde, (**52b**) with atomic labeling scheme and H atoms are shown as small spheres of arbitrary radii is shown in (**Figure 3.6**).

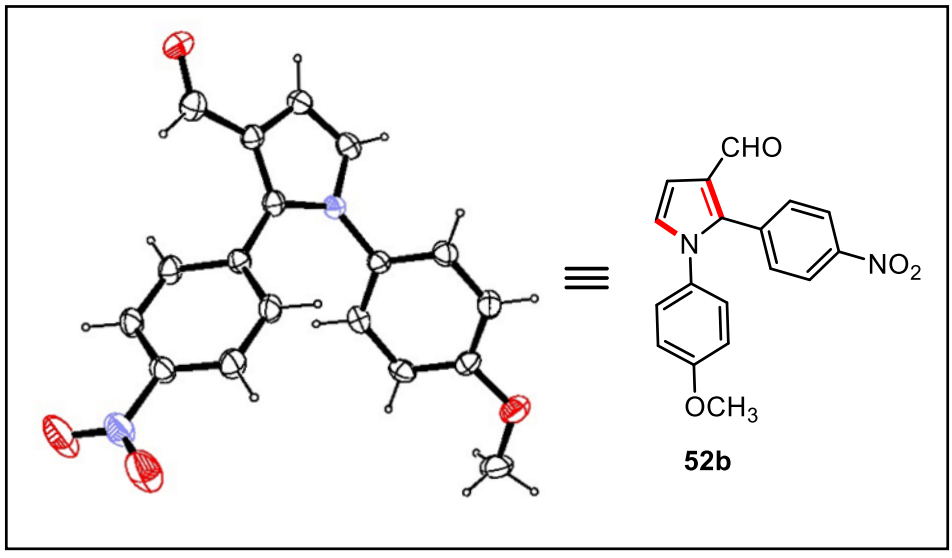


Figure 3.6 Single-crystal X-ray analysis of **52b**

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Chapter IV

Proline catalyzed direct synthesis of densely substituted-3-formylpyrroles

4.1 Introduction

Heterocyclic compounds have attracted great attention for their important activities and a wide range of applications in a variety of biological environments. From a synthetic standpoint, the ability to assemble these heterocycles from simple precursors in an atom- and step-economic manner would be highly rewarding. Among the nitrogen heterocycles, pyrrole based skeleton is widely distributed in a drug like compounds, bioactive natural products, synthetic medicinal agents and shows important applications in materials science.[1-21] Pyrrole and their derivatives are considered as one of the most pharmaceutically important class of *N*-heterocyclic compounds because of their remarkable anti-bacterial,[22] anti-viral,[23] anti-inflammatory,[24] anti-tumor,[25] antioxidant activities,[26] immunosuppressive and anticancer agents.[27] Moreover, polypyrroles have been applied as conducting polymers,[28-29] pyrrolic macrocycles as anion receptors, such as calyx [4] pyrroles, [30-36] promising pharmacophores in medicinal chemistry,[37-38] and agrochemicals**.**[39-42] Polysubstituted pyrroles such as Neolamellarin A, a metabolite isolated from the sponge Dendrilla nigra, demonstrated antitumor activity.[43] Pyrrolnitrin functions as a systemic antifungal agent.[44] Fludioxonil is a contact broad-spectrum fungicide structurally related to pyrrolnitrin.[45] Licofelone possesses significant analgesic, anti-inflammatory, and antiasthmatic activities.[46] Apricoxib, a cyclooxygenase-2 (COX-2) inhibitor, exhibited antitumor activity.[47] The development of efficient methods to construct polysubstituted pyrroles has been attracting considerable interest due to the potential applications of this kind of compounds and has emerged as an attractive synthetic motif since it is frequently found in natural products (**Figure 4.1**) and compounds incorporating such a motif possess several types of bioactivities.

Due to the high commercial impact of substituted pyrroles, a series of efficient methods including classical one's have been developed by synthetic chemists.[48-51] Cycloaddition reactions,[52] multi-component reactions,[53-54] metal-catalyzed transformations [55] and various other synthetic approaches [56-68] which are predominantly applied strategies to provide easy access to pyrroles. However, most of these methods are limited to the use of elaborately designed starting materials, suffer from low efficiency and selectivity and sometimes required harsh conditions. Here in this chapter, we described few methods in which polysubstituted pyrroles have been synthesized involving these above-mentioned methods.

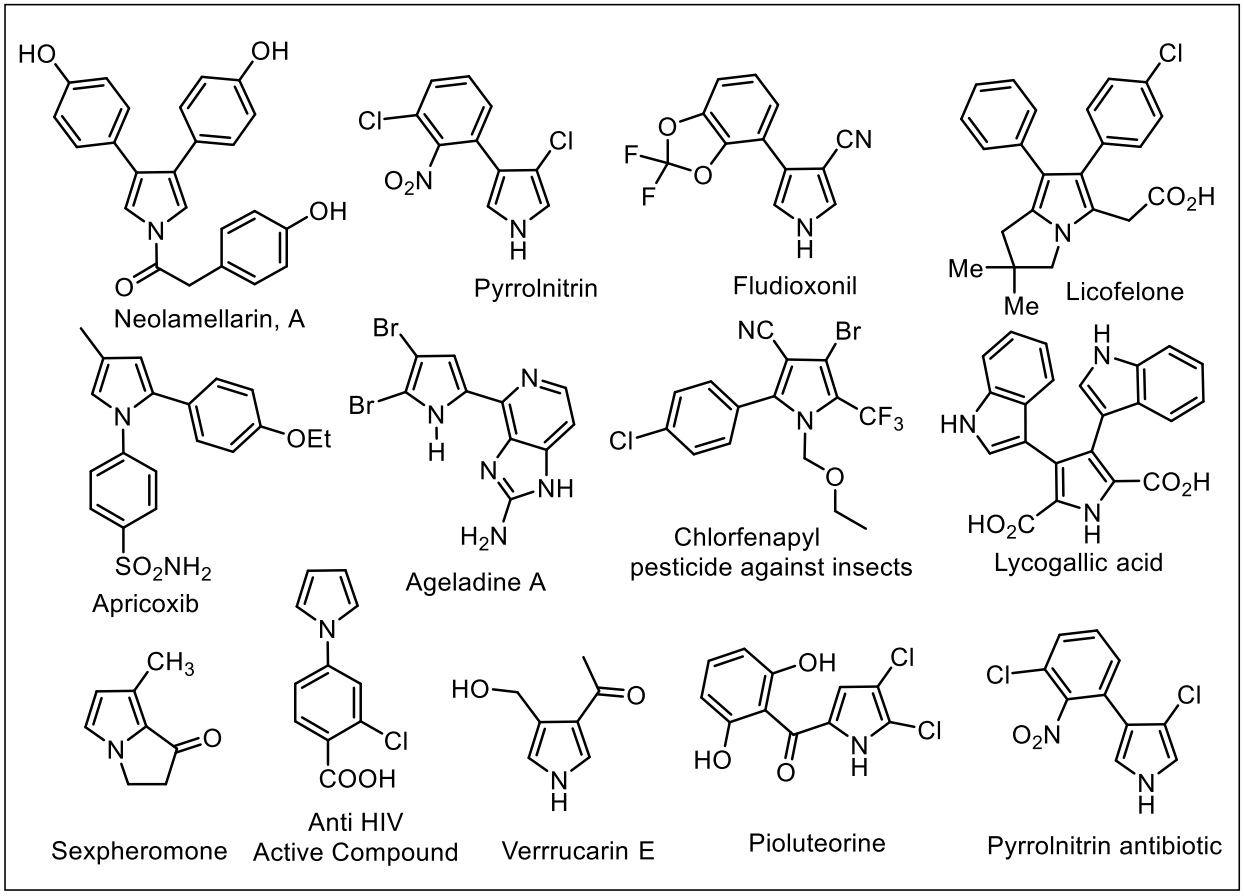
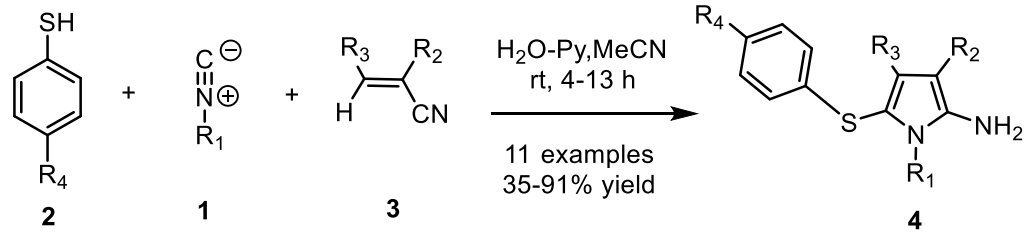


Figure 4.1 Bioactive natural products containing pyrrole core

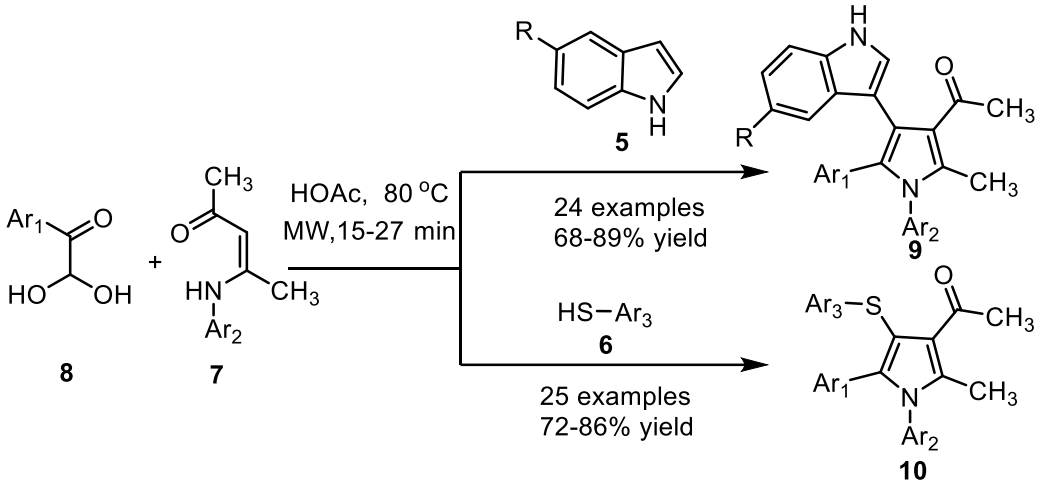
For example Mironov group described the preparation of 2-amino-5-arylthiopyrroles (**4**) starting from isocyanides (**1**), thiophenols (**2**) and gem-diactivated olefins (**3**) under basic conditions (**Scheme 4.1**).[69] It was observed that when olefin bearing an alkyl group such as R_3 then there is a decrease in the reaction time and an increase in reaction yield. It was also found that the use of aliphatic thiols was not successful.



Scheme 4.1 Synthesis of fully substituted 2-amino-5-arylthiopyrroles

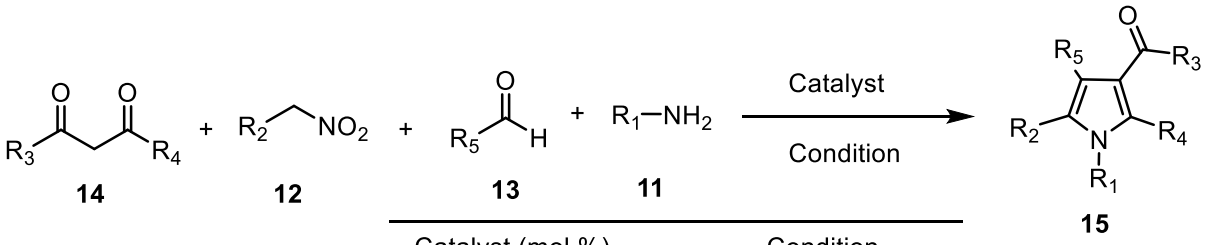
Tu *et al.* reported related three-component pyrrole synthesis that allows the incorporation of nucleophilic moieties into the pyrrole C-4 position.[70] This method is based on the microwave-

promoted reaction between indoles (**5**) or benzenethiol (**6**) with *β*-enaminones (**7**) and aryl glyoxal monohydrates (**8**) in the presence of acetic acid in good to excellent yields (**Scheme 4.2**).



Scheme 4.2 Indolation and thiolation-based three-component pyrrole synthesis

Four-component versions towards the synthesis of fully substituted pyrroles (**15**) has been widely investigated by reacting together nitroalkanes (**12**), aldehydes (**13**), 1, 3-dicarbonyl compounds (**14**) and primary amines (**11**) in the presence of different catalysts, including $FeCl_3$,[71] I_2,[72] nickel chloride hexahydrate,[73] silica gel supported tungstic acid (STA),[74] montmorillonite clay,[75] CuO nanoparticles [76] and gluconic acid aqueous solution (GAAS)[77] (**Scheme 4.3**).

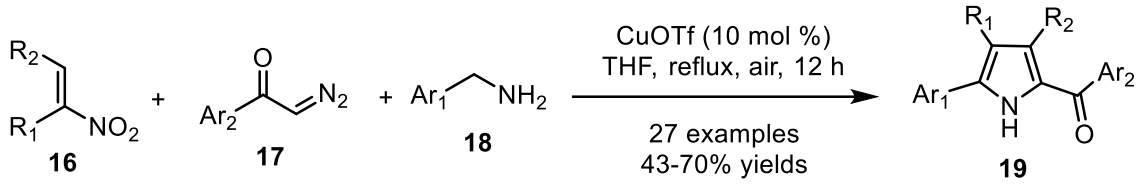


Catalyst (mol %)	Condition
$FeCl_3$ (10)	Reflux, 5-16 h
I_2	90-95 °C, 6-8 h
$NiCl_2.6H_2O$ (10)	Reflux, 6-12 h
STA (10)	Reflux, 4-6 h
Montmorillonite clay K_{10} or KSF	60 °C, 5-8 h
Nano CuO (10)	100-105 °C, 12 h
GAAS (50 wt %)	100 °C, 3-48 h

Scheme 4.3 Four-component synthesis of pyrroles from nitroalkanes, and dicarbonyl compounds

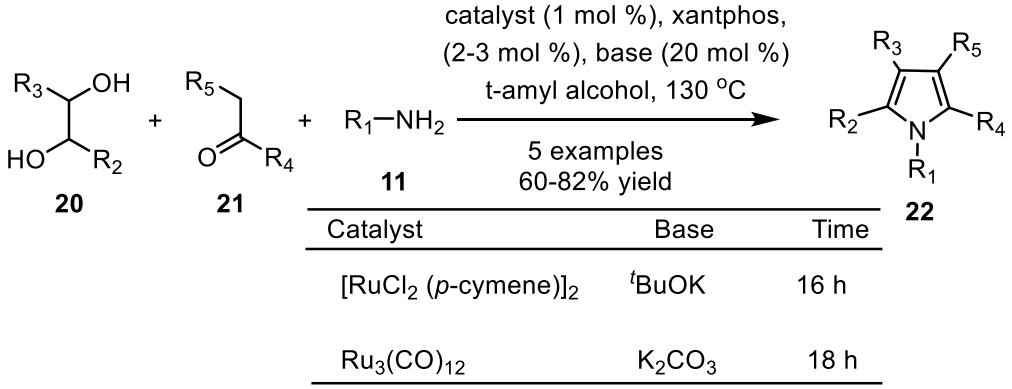
Wang and coworkers demonstrated the copper-catalyzed three-component reaction of α-diazoketones (**17**), nitroalkenes (**16**), and amines (**18**) under aerobic conditions towards the

synthesis of polysubstituted pyrroles (**19**). The cascade process involves an N-H insertion of carbene, a copper-catalyzed oxidative dehydrogenation of amine, and a [3+2] cycloaddition of azomethine ylide. The reaction involves the assembling of the pyrrole core from [1+ 2+ 2] atom fragments as shown in (**Scheme 4.4**).[78]



Scheme 4.4 Copper-catalyzed multicomponent synthesis of pyrrole

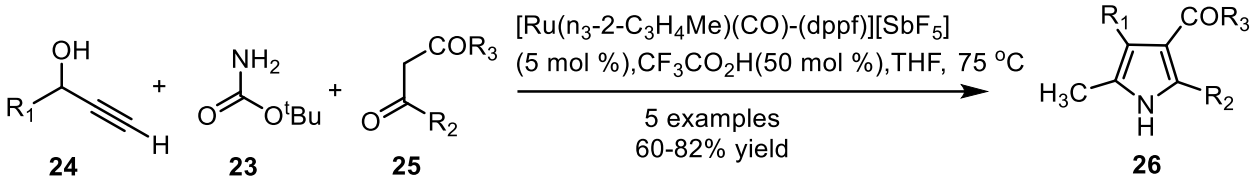
Recently, the group of Beller has reported the three component combinations of ketones (**21**), amines (**11**) and diols (**20**) in the presence of ruthenium catalytic systems as a highly regioselective route to polysubstituted pyrroles (**22**), with water as the only side product. They studied two different combinations of the ruthenium catalyst and base,[79-80] both of which showed similar efficiencies in terms of yields, as shown in (**Scheme 4.5**). When non-symmetrical diols were used, very high or complete regioselectivities were achieved, whereby the C–H alkylation occurs at the more reactive, sterically less hindered position of the diol.



Scheme 4.5 Three-component ruthenium-promoted pyrrole synthesis reported by Beller

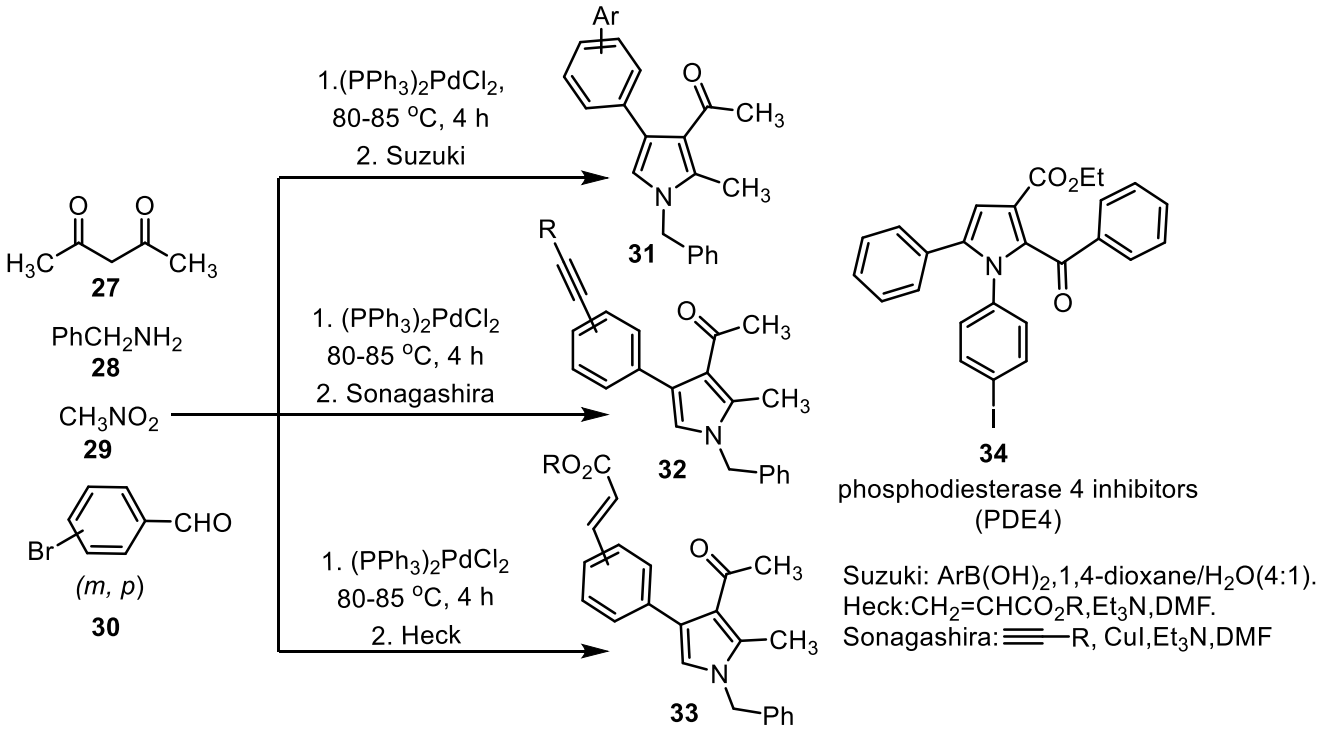
Cadierno and Gimeno have described a three-component pyrrole (**26**) synthesis by reaction between *tert*-butyl carbamate (**23**), propargyl alcohols (**24**) and β-dicarbonyl compounds (**25**) in the presence of the 16-electron allyl-ruthenium (II) complex [Ru(η_3-2-C_3H_4Me)(CO)-(dppf)] [SbF_5], where dppf is 1, 10-bis(diphenyl phosphinyl) ferrocene (**Scheme 4.6**).[81] This reaction is an extension of previous work by the same group based on the use of primary amines which was very slow when using ammonia and was therefore not amenable to the preparation of *N*-unsubstituted pyrroles.[82] The use of *tert*-butyl carbamate as the source of the pyrrole nitrogen

atom was inspired in previous work by Zhan, who achieved a similar transformation using indium trichloride as the catalyst.[83] Iodine was subsequently found to be a suitable catalyst for the reaction.[84]



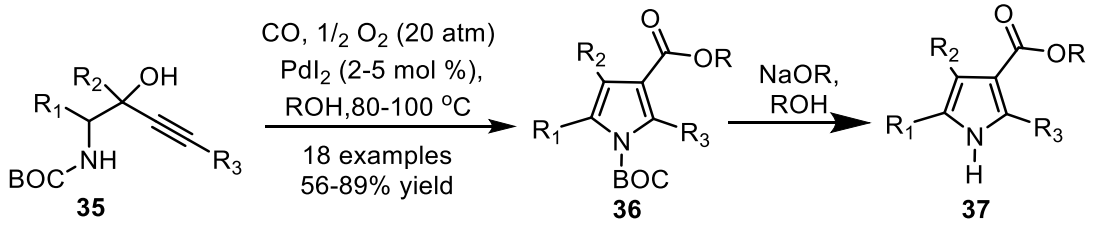
Scheme 4.6 Synthesis of pyrroles from tertbutyl carbamate, propargyl alcohols and β-dicarbonyl compounds

Manojit Pal and coworkers discovery allowed telescoping the multicomponent pyrrole synthesis with several Pd-catalyzed cross-coupling reactions, including Heck, Suzuki and Sonogashira coupling in a single pot for the synthesis of functionalized pyrroles (**31-33**) from nitroalkanes (**29**), aldehydes (**30**), 1,3-dicarbonyl compounds (**27**) and primary amines (**28**) in the presence of catalyst $(PPh_3)_2PdCl_2$ (**Scheme 4.7**).[85] Hence these pyrroles obtained are potential inhibitors of phosphodiesterase 4 inhibitors (PDE4) (**34**).[86]



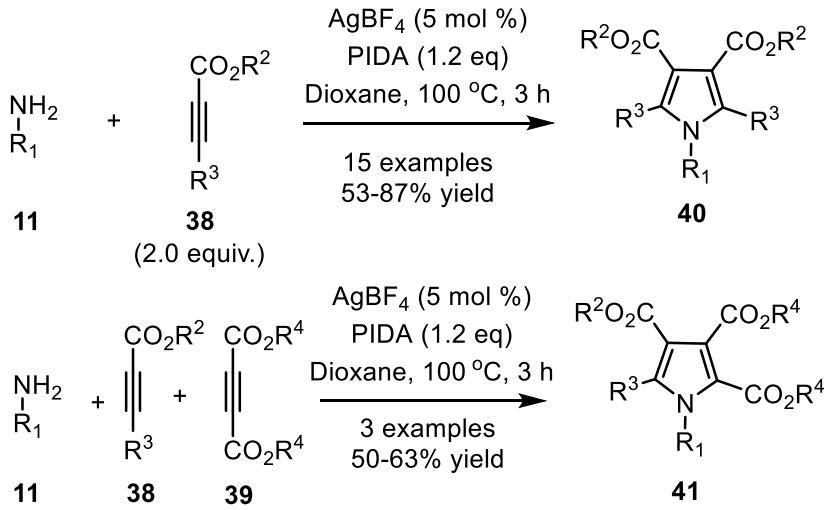
Scheme 4.7 Combination of pyrrole synthesis with Pd-catalyzed cross-coupling reactions in a one-pot transformation and related precursor to phosphodiesterase 4 inhibitors

Gabriele *et al.* has reported a novel and convenient approach to functionalized pyrroles (**36**) based on an intramolecular Pd-catalyzed oxidative heterocyclization-alkoxycarbonylation domino process of readily available *N*-Boc-1-amino-3-yn-2-ols (**35**). Reactions were carried out in alcoholic solvents at 80−100 °C and under 20 atm (at 25 °C) of a 4:1 mixture of CO-air, in the presence of the PdI_2-KI catalytic system (2−5 mol % of PdI_2, KI/PdI_2 molar ratio = 10) (**Scheme 4.8**).[87] This mixture could be conveniently and quantitatively converted into deprotected pyrrole-3-carboxylic esters (**37**) by a simple basic treatment.



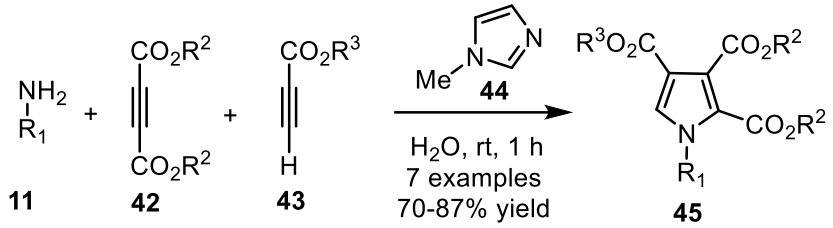
Scheme 4.8 Pd-catalyzed oxidative hetero cyclization–alkoxy carbonylation domino process

Jiang and coworkers demonstrated the addition/oxidative cyclization of alkynes (**38** and **39**) with amines (**11**) in the presence of silver tetrafluoroborate ($AgBF_4$) which was employed as a Lewis acid catalyst and phenyl iodonium diacetate (PIDA) oxidant leads to formation of polysubstituted pyrroles (**40** and **41**).[88] The reaction corresponds to the construction of a pyrrole fragment, which also provides a new way to the formation of C-C bonds. The reaction was quite general in terms of the amine substituent, which could be aliphatic or aromatic. Interestingly, the Jiang method offers the possibility to obtain reasonable yields of products in some cases arising from the use of crossed alkynoates (**Scheme 4.9**).



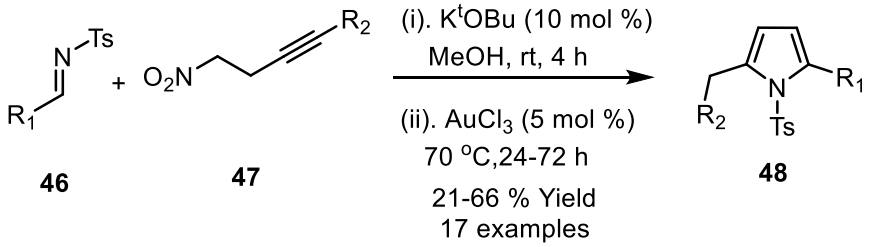
Scheme 4.9 Synthesis of polysubstituted pyrroles from various alkynoates and amines

Sayyed-Alangi reported a related organocatalyzed reaction that allows the use of two differently activated acetylenes. Thus, the reaction between primary amines (**11**), propiolates (**43**) and acetylene dicarboxylate (**42**) in the presence of *N*-methylimidazole (**44**) in water afforded non-symmetrical pyrrole-2,3,4-tricarboxylate derivatives (**45**) in good yields (**Scheme 4.10**).[89]



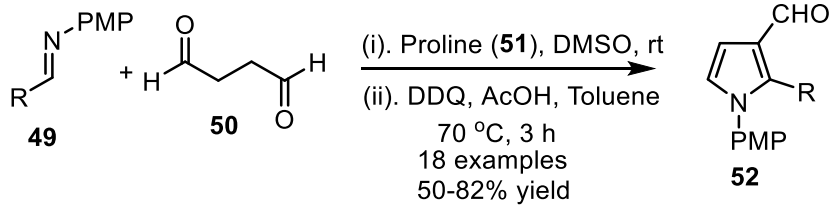
Scheme 4.10 Sayyed-Alangi's three-component synthesis of pyrrole-2, 3, 4-tricarboxylates

Dixon *et al*. reported an efficient, one-pot nitro-Mannich/hydroamination cascades for the direct synthesis of 2, 5-disubstituted pyrroles (**48**) from *p*-toluenesulfonyl protected imines (**46**) and 4-nitrobut-1-yne (**47**) under a combination of base and gold (III) catalysis (**Scheme 4.11).**[90]



Scheme 4.11 One-pot nitro-Mannich/hydroamination cascade sequence for pyrrole synthesis

Recently our group presented the two-pot synthesis of pyrrole-3-carboxaldehyde (**52**) using organocatalytic [3+2] annulations between succinaldehyde (**50**) and *N*-PMP imines(**49**) followed by oxidative aromatization using DDQ as an oxidant (**Scheme 4.12**). [91]

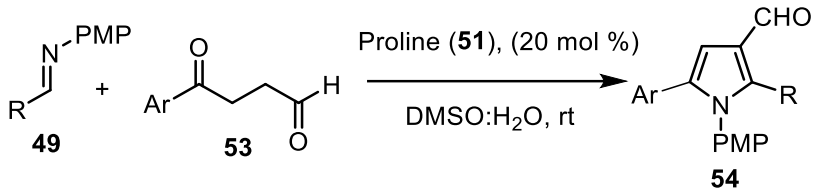


Scheme 4.12 Synthesis of pyrrole from succinaldehyde and imine

The novelty and clear synthetic potential of this method prompted us to explore similar transformation with 1, 4-ketoaldehydes to direct access of tetra-substituted pyrroles having formyl functionality at a C3 position under mild condition. Since a wider variety of ketoaldehydes is easily accessible, this can increase the potential diversity of the resulting

polysubstituted pyrroles. Interestingly, Paal–Knorr strategy is the only method to synthesize pyrroles from 1, 4-dicarbonyl compounds and ammonia or primary amines, and the development of the alternative method is highly inspiring. Hence, the development of a completely organocatalytic approach for highly functionalized non-chiral scaffolds would be very interesting from a synthetic as well as an environmental point of view. We recently developed an efficient one-pot synthesis of highly substituted pyrrole.[92]

Herein, we described our success on the fully organocatalytic one-pot direct synthesis of densely substituted 3-formylpyrroles (**54**) as most rational and straightforward route from versatile starting materials from 1, 4-ketoaldehyde (**53**) and *N*-PMP imines (**49**) (**Scheme 4.13).**

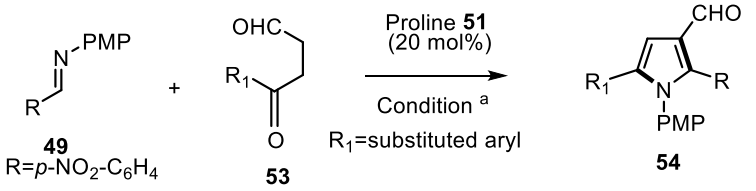


Scheme 4.13 Organocatalytic strategy for 3-formylpyrroles from 1, 4-dicarbonyls and imines

4.2 Results and Discussion

The initial screening of best reaction conditions with *N*-PMP imine (**49**) as model substrate was investigated and summarized in **Table 4.1**. We tried our initial experiment in DMSO using proline (**51**) as amine catalyst. To our delight, tetra-substituted pyrrole (**54**) was obtained directly with moderate yield in a one-pot sequence (**entry 1, Table 4.1**). The reaction proceeds through the chemoselective Mannich reaction of 1, 4-ketoaldehyde (**53**) with imine (**49**) followed intramolecular cyclization and aerobic oxidative aromatization. Next we made efforts to optimize the reaction condition to improve the reaction yields. Screening the reaction solvents exposed that most of them afforded reactions yields lower than that in DMSO (20–45%, **entries 2–6, Table 4.1**). Addition of water enhance the rate of reaction, pyrrole (**54**) was obtained in high yield (70%) in the presence of water (100 µL) (**entry 7, Table 4.1**), whereas any increment in the amount of water (200 µL) further reduced the reaction yields (**entry 8, Table 4.1**). Thus, we preferred to perform this one-pot strategy with the optimized conditions (**entry 7, Table 4.1**).

Table 4.1 Optimization of reaction conditions for the synthesis of (**54**)[a]

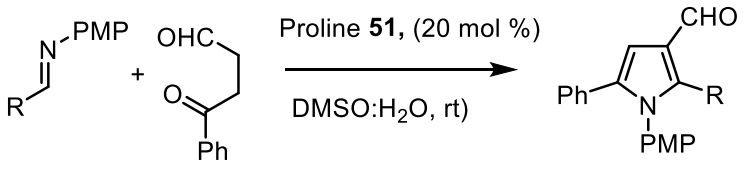


Entry	Conditions[a]	Yield (%)[b]
1	DMSO, rt, 48 h	58
2	DMF, rt, 26 h	45
3	CH_3CN, rt, 30 h	41
4	Toluene, rt, 24 h	n.r.
5	THF, rt, 28 h	34
6	CH_2Cl_2, rt, 28 h	<20
7[c]	**DMSO, rt, 24 h**	**70**
8[d]	DMSO, rt, 24 h	62

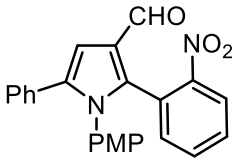
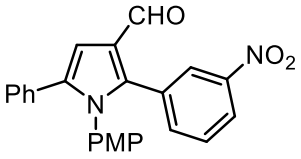
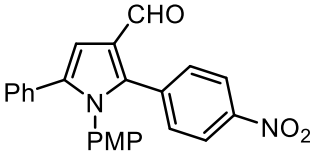
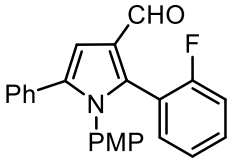
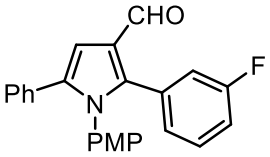
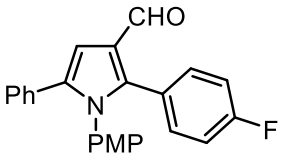
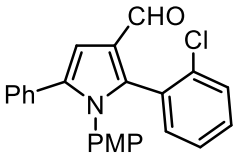
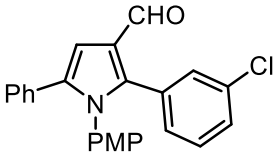
[a] Imine **49** (0.3 mmol), **53** (0.9 mmol), proline **51** (20 mol %), solvent (3.0 mL). [b] Isolated yield refer to **49**. [c] With the addition of H_2O (100 µL). [d] With the addition of water (200 µL).

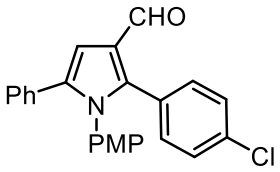
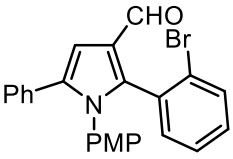
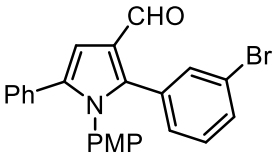
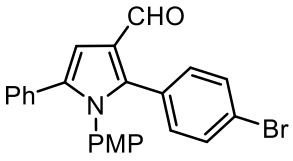
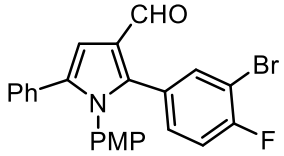
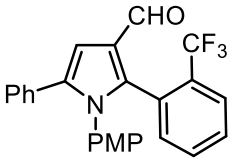
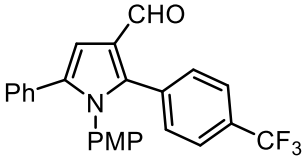
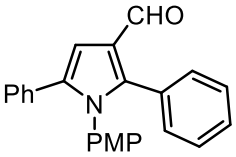
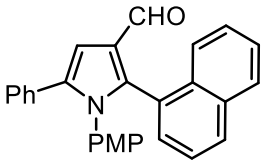
With the established reaction conditions in hand, a series of imines (**49**) were investigated for extending the substrate scope (**Table 4.2**). In general, all the *N*-PMP aldimines derived from corresponding aromatic aldehydes worked well in the reaction and provided a series of 2, 5-biaryl-3-formylpyrroles (**54**) in moderate to high yields (up to 70%). In case of electron-deficient arylimines reactions proceeded nicely (**entries 1–15 and 26-29 Table 4.2**), however the reactions were rather slow in case of imines derived from 2- substituted aldehydes (**entries 1, 4, 7, 10 14 and 26, Table 4.2**) and naphthaldehydes (**entries 17 and 18, Table 4.2**) lead to lower yields, perhaps because of the steric crowding. Not only simple aryl imine (**entry 16, Table 4.2**) but hetero-aryl imines also resulted in products with good yields (**entry 18–24, Table 4.2**). In the case of slightly electron-rich aryl imine (**entry 25, Table 4.2**), the corresponding pyrrole (**54y**) was obtained with moderate yield (45%). All the products were characterized with spectroscopic data.

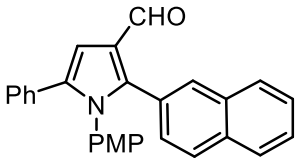
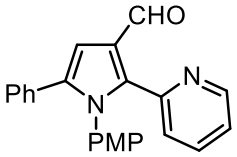
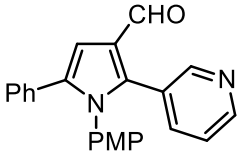
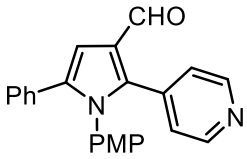
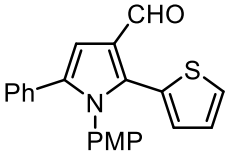
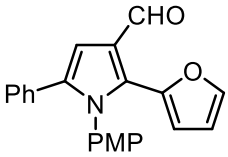
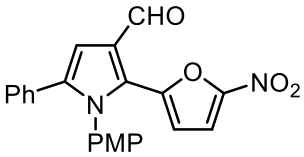
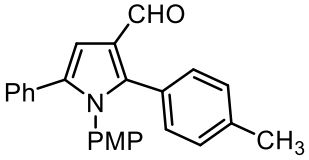
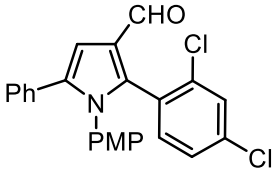
Table 4.2 Substrate scope for the synthesis of densely substituted pyrroles from various imines[a]

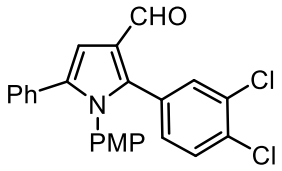
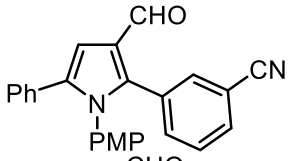
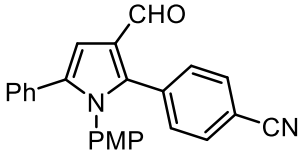


49 **53** **54**

Entry	R	Product	**54**	% Yield[b]
1	2-NO_2-C_6H_4		**54a**	67
2	3-NO_2-C_6H_4		**54b**	65
3	4-NO_2-C_6H_4		**54c**	70
4	2-F-C_6H_4		**54d**	69
5	3-F-C_6H_4		**54e**	65
6	4-F-C_6H_4		**54f**	70
7	2-Cl-C_6H_4		**54g**	61
8	3-Cl-C_6H_4		**54h**	63

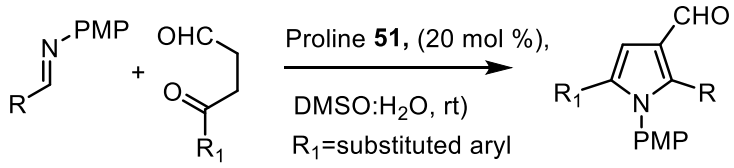
Entry	R	Product	54	% Yield[b]
9	4-Cl-C_6H_4		**54i**	67
10	2-Br-C_6H_4		**54j**	60
11	3-Br-C_6H_4		**54k**	65
12	4-Br-C_6H_4		**54l**	67
13	3-Br,4F-C_6H_3		**54m**	65
14	2-CF_3-C_6H_4		**54n**	66
15	4-CF_3-C_6H_4		**54o**	69
16	C_6H_5		**54p**	58
17	1-napthyl		**54q**	56

Entry	R	Product	54	% Yield[b]
18	2-napthyl		**54r**	60
19	2-pyridyl		**54s**	62
20	3-pyridyl		**54t**	55
21	4-pyridyl		**54u**	61
22	2-thienyl		**54v**	52
23	2-furyl		**54w**	50
24	5-NO_2, 2-furyl		**54x**	70
25	4-CH_3-C_6H_4		**54y**	45
26	2-Cl,4Cl-C_6H_3		**54z**	57

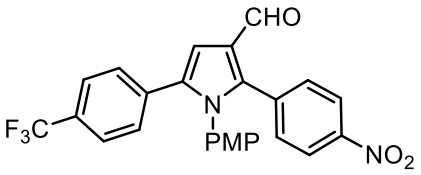
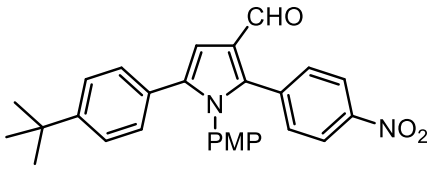
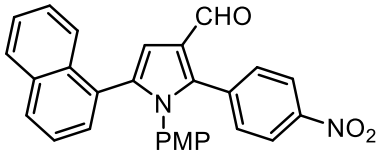
Entry	R	Product	54	% Yield[b]
27	3-Cl,4Cl-C_6H_3		**54aa**	55
28	3-CN-C_6H_4		**54ab**	65
29	4-CN-C_6H_4		**54ac**	69

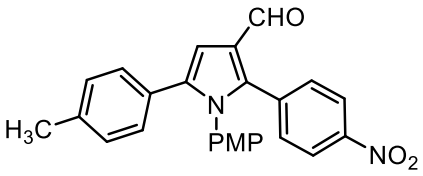
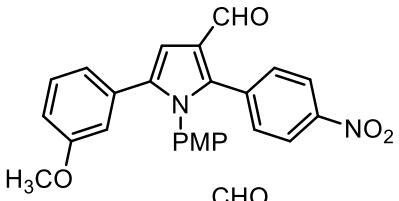
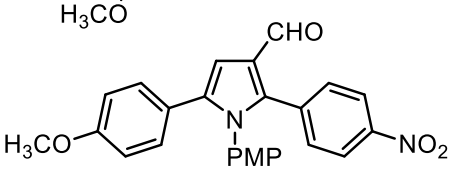
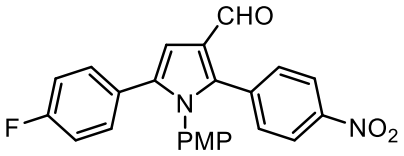
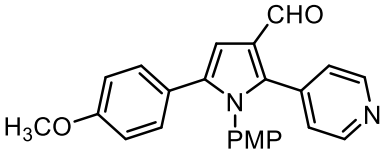
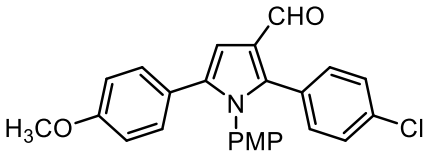
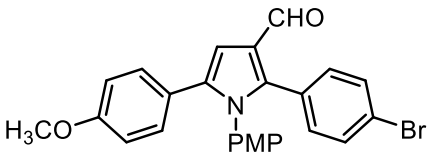
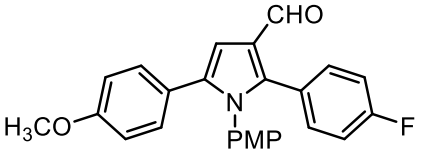
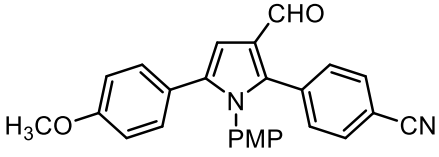
[a](i) Imine **49** (0.3 mmol), **53** (0.9 mmol), proline **51** (20 mol %), DMSO (3.0 mL), H_2O (100 µL). the [b]Isolated yield of **54**; about <10% of the corresponding aldehyde was obtained in all the cases due to cleavage of imine **49**.

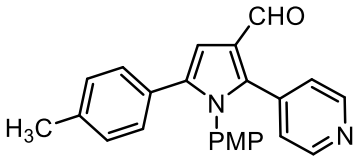
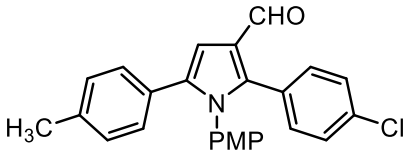
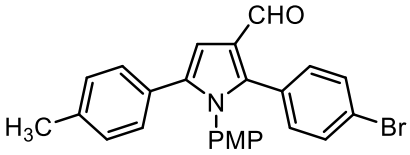
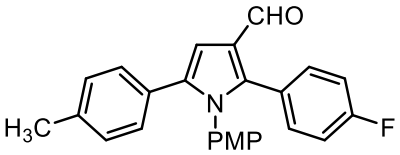
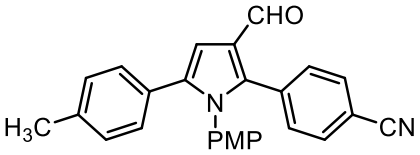
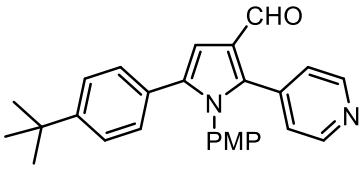
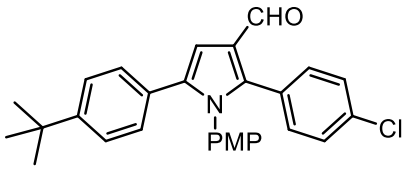
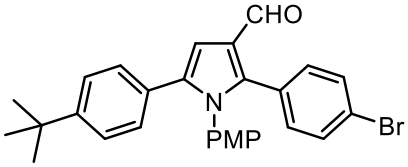
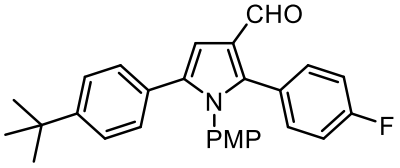
Table 4.3 Scope study with different 1, 4-keto-aldehydes and various imines

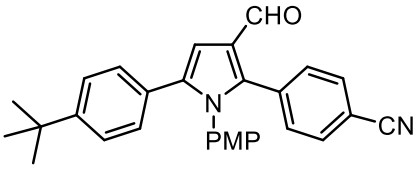
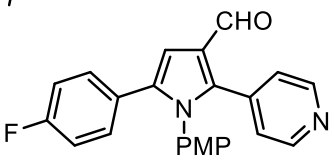
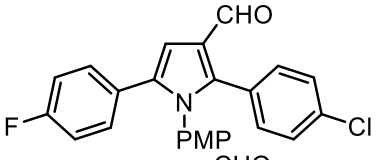
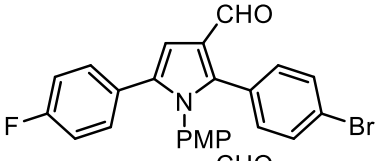
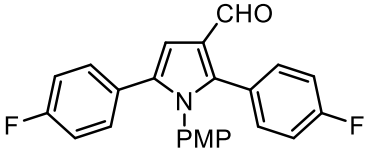
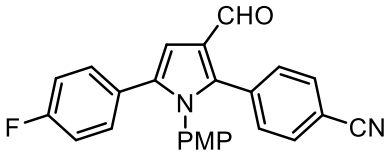
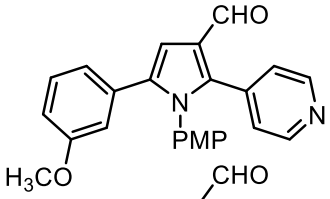
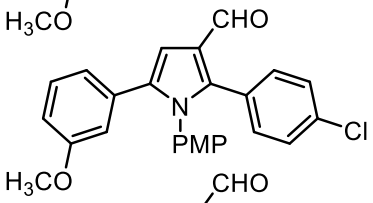
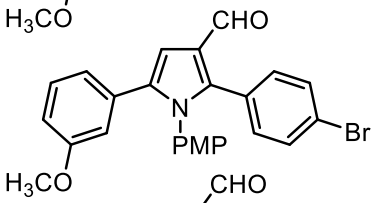
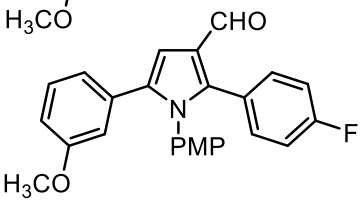


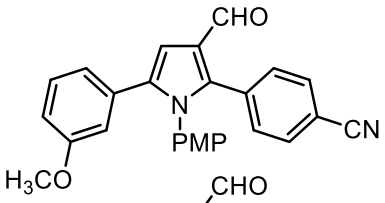
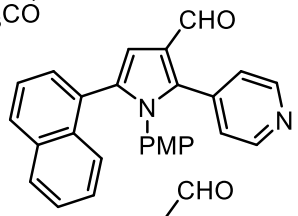
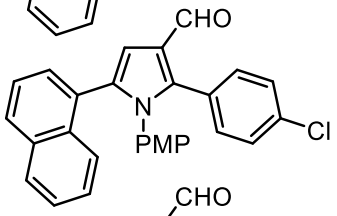
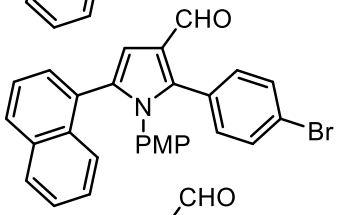
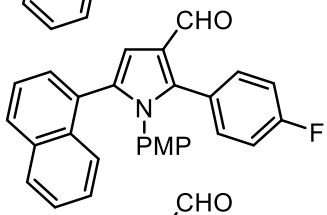
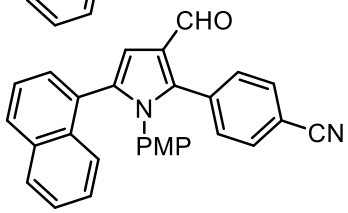
49 **53** **55**

Entry	R_1	R	Product	55	% Yield[b]
1	4-CF_3-C_6H_4	4-NO_2-C_6H_4		**55a**	64
2	4-$CH(Me)_3$-C_6H_4	4-NO_2-C_6H_4		**55b**	65
3	1-napthyl	4-NO_2-C_6H_4		**55c**	70

Entry	R_1	R	Product	**55**	% Yield[b]
4	4-CH_3-C_6H_4	4-NO_2-C_6H_4		**55d**	69
5	3-OMe-C_6H_4	4-NO_2-C_6H_4		**55e**	64
6	4-OMe-C_6H_4	4-NO_2-C_6H_4		**55f**	65
7	4-F-C_6H_4	4-NO_2-C_6H_4		**55g**	62
8	4-OMe-C_6H_4	4-pyridyl		**55h**	60
9	4-OMe-C_6H_4	4-Cl-C_6H_4		**55i**	62
10	4-OMe-C_6H_4	4-Br-C_6H_4		**55j**	65
11	4-OMe-C_6H_4	4-F-C_6H_4		**55k**	66
12	4-OMe-C_6H_4	4-CN-C_6H_4		**55l**	68

Entry	R_1	R	Product	**55**	% Yield[b]
13	4-CH_3-C_6H_4	4-pyridyl		**55m**	58
14	4-CH_3-C_6H_4	4-Cl-C_6H_4		**55n**	62
15	4-CH_3-C_6H_4	4-Br-C_6H_4		**55o**	65
16	4-CH_3-C_6H_4	4-F-C_6H_4		**55p**	66
17	4-CH_3-C_6H_4	4-CN-C_6H_4		**55q**	68
18	4-$CH(Me)_3$-C_6H_4	4-pyridyl		**55r**	63
19	4-$CH(Me)_3$-C_6H_4	4-Cl-C_6H_4		**55s**	64
20	4-$CH(Me)_3$-C_6H_4	4-Br-C_6H_4		**55t**	66
21	4-$CH(Me)_3$-C_6H_4	4-F-C_6H_4		**55u**	65

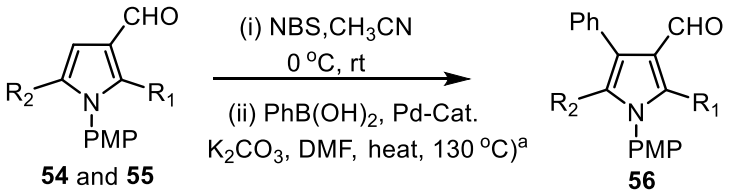
Entry	R_1	R	Product	55	% Yield[b]
22	4-$CH(Me)_3$-C_6H_4	4-CN-C_6H_4		**55v**	69
23	4-F-C_6H_4	4-pyridyl		**55w**	58
24	4-F-C_6H_4	4-Cl-C_6H_4		**55x**	60
25	4-F-C_6H_4	4-Br-C_6H_4		**55y**	63
26	4-F-C_6H_4	4-F-C_6H_4		**55z**	65
27	4-F-C_6H_4	4-CN-C_6H_4		**55aa**	66
28	3-OCH_3-C_6H_4	4-pyridyl		**55ab**	61
29	3-OCH_3-C_6H_4	4-Cl-C_6H_4		**55ac**	63
30	3-OCH_3-C_6H_4	4-Br-C_6H_4		**55ad**	65
31	3-OCH_3-C_6H_4	4-F-C_6H_4		**55ae**	67

Entry	R_1	R	Product	55	% Yield[b]
32	3-OCH_3-C_6H_4	4-CN-C_6H_4		**55af**	68
33	1-napthyl	4-pyridyl		**55ag**	50
34	1-napthyl	4-Cl-C_6H_4		**55ah**	54
35	1-napthyl	4-Br-C_6H_4		**55ai**	55
36	1-napthyl	4-F-C_6H_4		**55aj**	56
37	1-napthyl	4-CN-C_6H_4		**55ak**	59

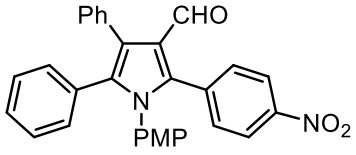
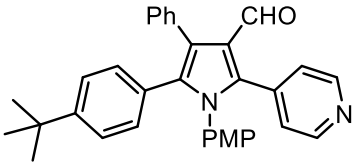
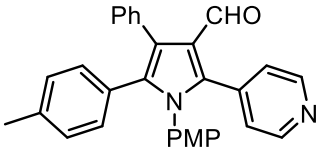
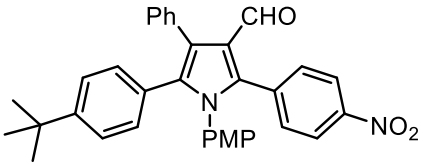
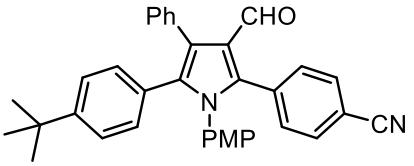
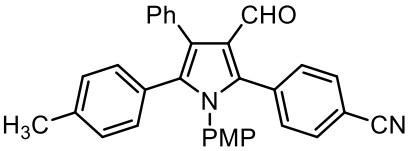
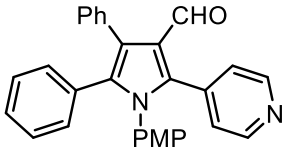
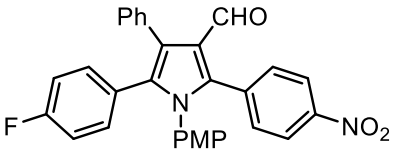
[a](i) Imine **49** (0.3 mmol), **53** (0.9 mmol), proline **51** (20 mol %), DMSO (3.0 mL), H_2O (100 µL). [b]Isolated yield of **55**; about <10% of the corresponding aldehyde was obtained in all the cases due to cleavage of imine **49**.

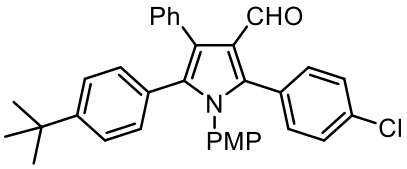
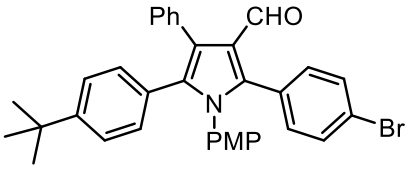
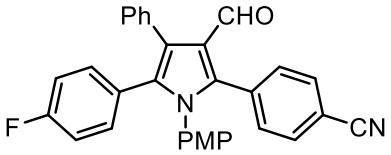
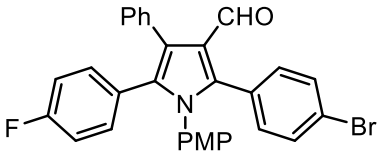
Next, differently substituted 2, 5-biaryl-3-formylpyrroles (**55a–55ak**) were prepared in good yields to show the substrate scope of 1,4-ketoaldehyde (**53**) (**Table 4.3**). It was found that the protocol works efficiently regardless to both electron deficient and electron-rich aromatic ring R_1 of (**53**).

Table 4.4 Synthesis of different fully substituted -3-formyl pyrrole product



54 and **55** → **56**

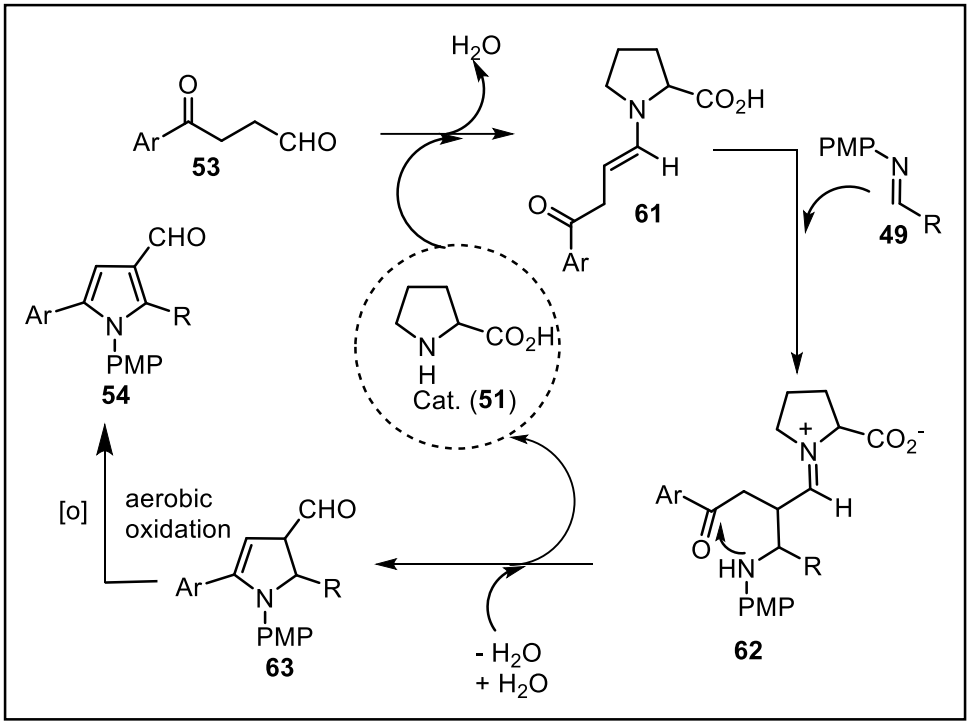
Entry	R_1	R_2	Product	**56**	% Yield[b]
1	C_6H_5	4-NO_2-C_6H_4		**56a**	74
2	4-$CH(CH_3)_3$-C_6H_4	4-pyridyl		**56b**	69
3	4-CH_3-C_6H_4	4-pyridyl		**56c**	72
4	4-$CH(CH_3)_3$-C_6H_4	4-NO_2-C_6H_4		**56d**	71
5	4-$CH(CH_3)_3$-C6H4	4-CN-C_6H_4		**56e**	68
6	4-CH_3-C_6H_4	4-CN-C_6H_4		**56f**	68
7	C_6H_5	4-pyridyl		**56g**	62
8	4-F-C_6H_4	4-NO_2-C_6H_4		**56h**	72

Entry	R_1	R_2	Product	**56**	% Yield[b]
9	4-$CH(CH_3)_3$-C_6H_4	4-Cl-C_6H_4		**56i**	66
10	4-$CH(CH_3)_3$-C_6H_4	4-Br-C_6H_4		**56j**	65
11	4-F-C_6H_4	4-CN-C_6H_4		**56k**	65
12	4-F-C_6H_4	4-Br-C_6H_4		**56l**	64

[a](i) Compound **54** and **55** (0.3 mmol), NBS (0.3 mmol), CH_3CN (3.0 mL), (ii) DMF (3.0 mL), Ph $B(OH)_2$ (0.3 mmol), Pd cat.(10 mol %).[b]Isolated yields of products **56** obtain in all the cases.

As these synthesized densely substituted formyl-3-pyrroles are useful synthetic intermediates that can be further functionalized by conventional methodologies such as coupling transformations to provide a diversity of fully substituted formyl-3-pyrroles (**56**) in good yields as shown in (**entry 1-12, Table 4.4**).

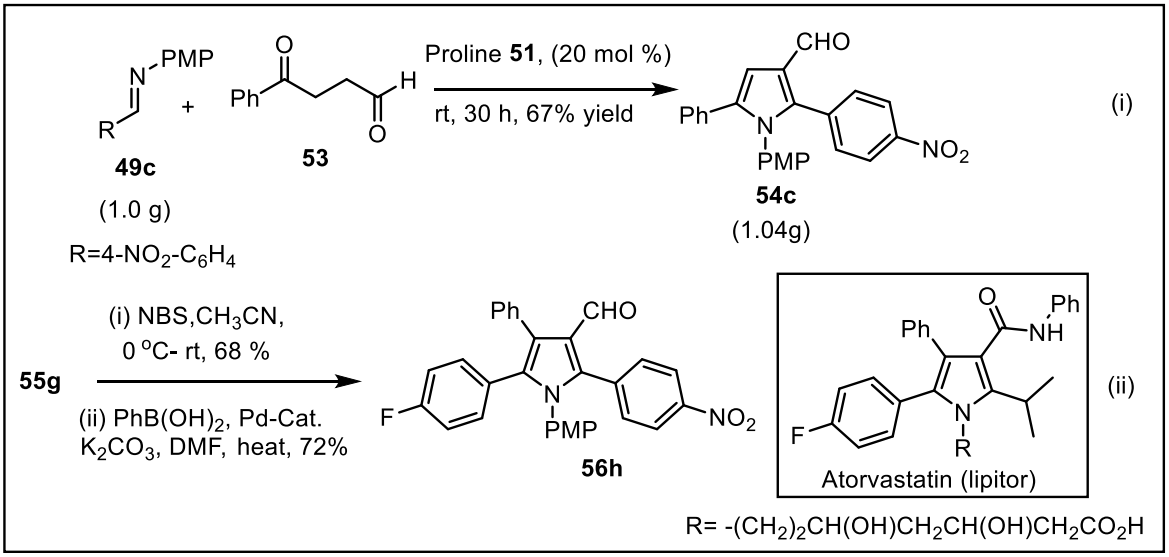
Based on our initial study and literature precedents on proline (**51**) catalyzed Mannich reaction, the following stepwise mechanism is proposed to account for this reaction. As shown in (**Scheme 4.14**), the *in situ* generated enamine (**61**), generated from 1, 4-ketoaldehyde (**53**) and proline (**51**), reacts with *N*-PMP imine (**49**) *via* a direct Mannich reaction to produce (**62**). The intermediate (**62**) undergoes intramolecular cyclization to enamine (**63**) with the simultaneous regeneration of proline (**51**). Enamine (**63**) underwent anaerobic oxidative aromatization to afford the densely substituted pyrrole 3-carboxaldehyde (**54**).



Scheme 4.14 Plausible mechanism of the cascade [3+2] annulation reaction for pyrrole synthesis

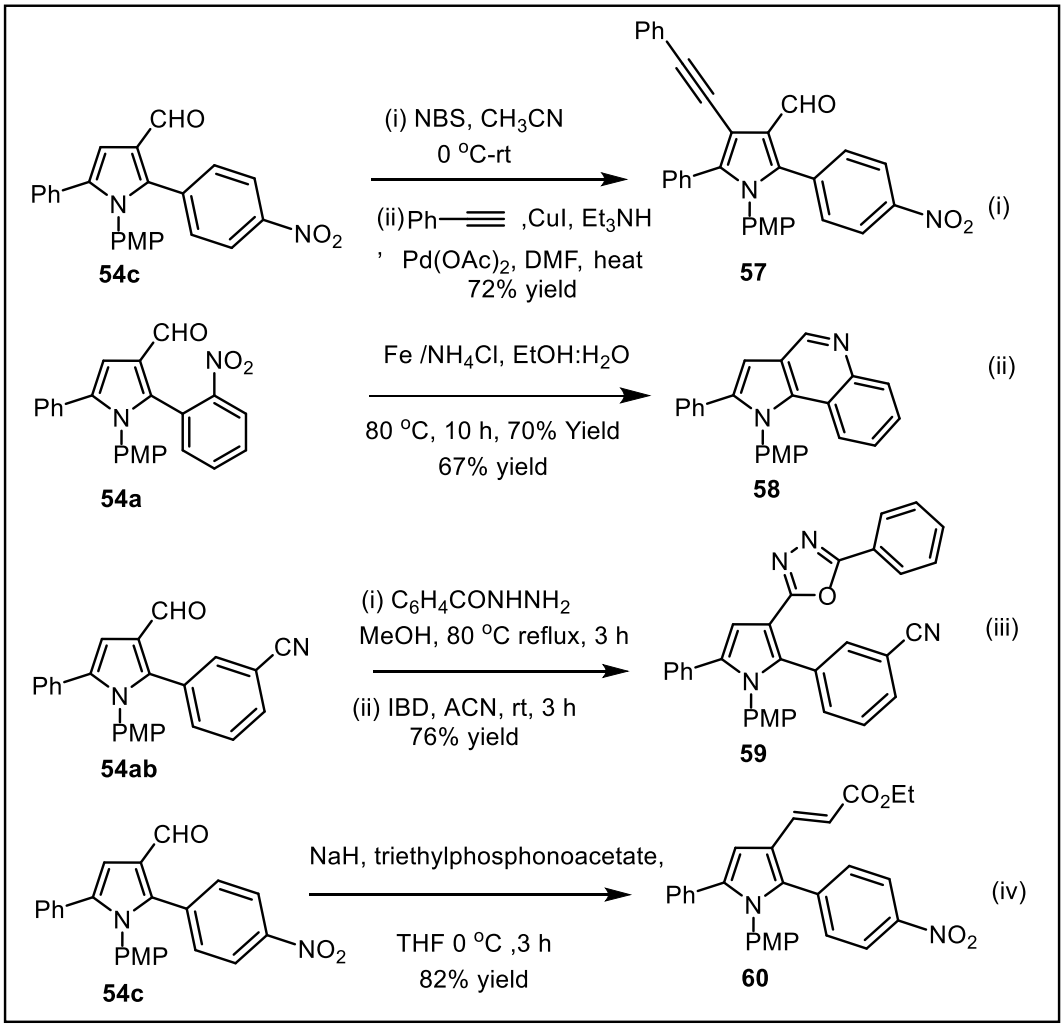
Furthermore, these pyrrole compounds can be converted into significantly important scaffolds which are having tremendous applications in biological systems.

- Gram scale synthesis of pyrrole (**54c**) (1.04 g, 67% yield) from aldimine (**49c)** (1.0 g) with an extended reaction time (**Eqn (1), Scheme 4.15**).



Scheme 4.15 Application at gram-scale and synthesis of fully substituted pyrrole

- A quick synthesis of fully substituted 3-formylpyrrole 5 through coupling sequence (**Eqn (2), Scheme 4.15**). Fully substituted pyrroles are versatile building blocks in organic synthesis and can be readily converted to biologically important products. For example; compounds (**56h**) contains the similar pyrrole skeleton of atorvastatin, a clinically approved drug.[93-95]
- Synthesis of fully substituted aryl 3-formyl pyrrole (**57**) was achieved through Sonagashira coupling protocol (**Eqn (i), Scheme 4.16**).[96-97]
- A reductive cyclization reaction of (**54a**) provided the corresponding pyrroloquinoline core containing natural product (**58**) in just one step which is not possible by any other process.[98] In this reaction reduction of nitro compound takes place in the presence of Fe/NH_4Cl in $EtOH:H_2O$ (4:1) followed by *in situ* imine formation producing corresponding pyrroloquinoline compound (**58**) with good yields (**Eqn (ii), Scheme 4.16**).



Scheme 4.16 Some application of densely substituted pyrroles

- The desired substituted pyrrole-oxadiazole fused hybrid product (**59**) was successfully prepared through the expected condensation of phenyl hydrazide and starting material (**54ab**) followed by IBD oxidation in the same vessel (**Eqn (iii), Scheme 4.16**).[99] A Wittig-reaction of (**54c)** provided the corresponding α, β-unsaturated ester (**60)**, with high yields (**Eqn (iv), Scheme 4.16**).[100]

4.3 Conclusions

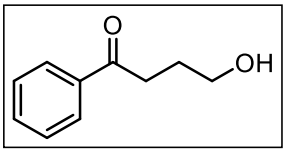
In summary, we have developed a straightforward synthesis of densely substituted 3-formylpyrroles (**54**) in a modular fashion from 1, 4-dicarbonyl compounds (**53**) and aldimines (**49**) under very mild condition. This one-pot cascade sequence involves chemoselective Mannich-cyclization-aerobic oxidation as formal [3+2] cycloaddition. The viability of this method was established; (i) at gram scale, (ii) synthesis of fully substituted 3-formylpyrrole, (iii) synthesis of pyrroloquinoline, pyrrole-oxadiazole, and pyrrole-acrylate based fused scaffolds which are having wide applications in medicinal as well as in material sciences. We believe that this method provides a rapid access to highly substituted 3-formylpyrroles, which are difficult to access by alternate approaches.

4.4 General Experimental Methods

All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on SiO_2 gel F-254 plates. Unless otherwise noted all reactions have been carried out with distilled and dried solvents. Oven (120 °C) dried glassware were used. All work up and purification was carried out with reagent grade solvents in the air. 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 on a BRUKER-AV400 (400 MHz and 75 MHz) spectrometer 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. Infrared (FT-IR) spectra were recorded on an ABB Bomen MB 3000 FTIR Spectrophotometer system using KBr pellets. Melting points were recorded in open glass capillary tubes on an MPA 120-automated melting point apparatus and are uncorrected.

4.5 General Experimental procedure for the synthesis of Hydroxy Ketones from Lactones[101]

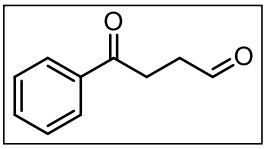
4.5.1 Synthesis of 4-Hydroxy-1-phenylbutan-1-one (64a)



Bromobenzene (1.81 g, 11.6 mmol, 1.0 equiv.) in dry THF (10.0 mL) was added dropwise with the help of syringe to a stirred solution of crushed magnesium turnings (0.56 g, 23.2 mmol, 2.0 equiv.) in dry THF (10 mL, freshly distilled from sodium/benzophenone) at room temperature for one hour under inert atmosphere. This prepared Grignard reagent solution was cooled at 0 °C and then added dropwise through the cannula to the stirred solution of butyrolactone (1.0 g, 11.6 mmol, 1 equiv.) in THF (10 mL) at 0 ºC over 30 minutes. The combined reaction mixture was stirred at 0 °C for additional 2 h and then quenched by NH_4Cl (15 mL, saturated) and the organic layer was separated. The aqueous layer was again extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (15 mL), dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by silica gel (100-200 mesh) column chromatography (Hexane: EtOAc, 20:1 to 5:1) to give the desired keto-alcohol (**64a**) as a white semi-solid (1.30 g, 68% yield).

1H NMR (400 MHz, $CDCl_3$) δ 1.89-1.96 (m, 2H), 3.05 (t, *J* = 7.0 Hz , 2H), 3.65 (t, *J* = 6.2 Hz, 2H), 3.98 (bs, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.52 (t, *J* = 7.4 Hz, 1H), 7.92 (d, *J* = 7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.53, 34.71, 62.32, 126.12 (2C), 128.12 (2C), 132.65, 146.82, 200.31; IR (KBr)/cm^{-1} 3379, 2939, 1766, 1172, 1033; HRMS (ESI): Calcd for $C_{10}H_{12}O_2$ (MH^+) 165.0916; Found 165.0921.

4.5.2 General Experimental procedure for the synthesis of 4-Oxo-4-phenylbutanal (64b)



4-Hydroxy-1-phenylbutan-1-one (**64a**) (0.5 g, 3.0 mmol, 1 equiv.) solution in dichloromethane (2.5 mL) was added to a stirred solution of PCC (0.98 g, 4.6 mmol, 1.5 equiv.) and celite (0.25 g) in dichloromethane (2.5 mL) and stirred for 3 hrs at room temperature. The reaction was monitored by TLC till completion. The reaction mixture was filtered over a pad of Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography (Hexane: EtOAc = 90:10 to 70:30) to give the desired product **(64b)** as a yellow oily liquid (0.272 g, 55% yield).

1H NMR (400 MHz, $CDCl_3$) δ 2.79-2.97 (m, 2H), 3.31 (t, *J* = 6.3Hz, 2H), 7.40-7.48 (m, 2H), 7.57 (t, *J* = 7.5 Hz, 1H), 7.98 (d, *J* = 7.6 Hz, 2H), 9.90 (s, 1H) ; 13C NMR (75 MHz, $CDCl_3$) δ 30.97, 37.54, 128.00 (2C), 128.60 (2C), 133.27, 136.37, 197.83, 200.70; IR (KBr)/cm^{-1}

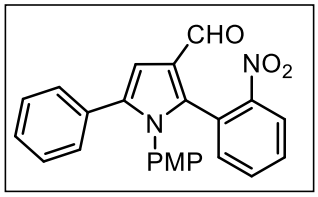
2923,1728, 1681, 1211, 979, 694; HRMS (ESI): Calcd for $C_{10}H_{10}O_2$ (MH^+) 163.0759; Found 163.0763.

4.6 Typical procedure for the synthesis of 2, 5-diaryl pyrrole-3-carboxaldehydes (**54**)

4-Oxo-4-phenylbutanal (**64b**) (0.9 mmol, 3M solution) was added to a mixture of preformed *N*-PMP aldimine (**49**) (0.3 mmol) and L-proline (**51**) (0.06 mmol) in DMSO (3.0 mL) at room temperature. The reaction mixture was stirred at room temperature until the aldimine (**49**) was consumed as monitored by TLC. The reaction was quenched with cold water (10 mL) and extracted with ethyl acetate (3 x 5 mL). The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The reaction mixture was purified through column chromatography by eluting the mixture of EtOAc/Hexane to give 2, 5-diaryl pyrrole 3-carbxaldehydes (**54**) with high yields up to (50-70%). In almost all the cases, we also obtained about ≤10% of aromatic aldehyde due to cleavage of corresponding imine under these conditions.

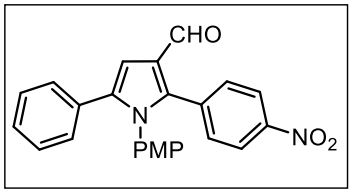
4.7 Characterization data of synthesized compounds (54a-54ac)

1-(4-methoxyphenyl)-2-(2-nitrophenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54a**)



Yellow pasty liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.80 (s, 1H),6.89 (d, *J* = 8.9, Hz, 2H), 7.06-7.08 (m, 2H), 7.12 (d, *J* = 8.9 Hz, 2H), 7.16-7.19 (m, 3H), 7.45-7.50 (m, 1H), 7.55-7.60 (m, 1H), 7.85 (d, *J* = 7.3 Hz, 2H), 9.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.41, 109.30, 114.61 (2C), 122.32, 125.96, 126.95, 128.03 (2C), 128.11 (2C), 128.31 (2C), 128.54 (2C), 129.35 (2C), 129.60, 131.80, 133.15, 136.14, 142.28, 159.58, 185.93; IR (KBr)/cm^{-1} 2932, 1674, 1512, 1250, 1173; HRMS (ESI): Calcd for $C_{24}H_{18}N_2O_4$ (MH^+) 399.1346; Found 399.1348.

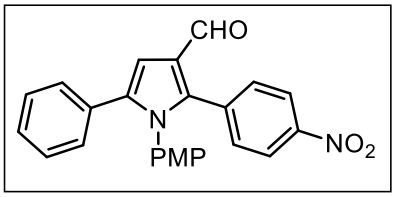
1-(4-methoxyphenyl)-2-(3-nitrophenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54b**)



Reddish brown solid (M.P = 154-155 ^{o}C); ^{1}H NMR (400) MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.98 (s, 1H), 7.10-7.12 (m, 2H), 7.21-7.24 (m, 3H) 7.39-7.46 (m, 2H) 8.08 (t, *J* = 1.7 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 9.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.33, 107.97, 114.33 (2C), 114.59, 123.20, 124.39, 125.76, 125.93, 127.54, 128.21(2C), 128.75 (2C), 129.56 (2C), 131.17, 131.33, 136.83,

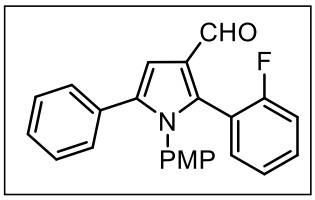
137.63,140.24 , 147.65, 159.23, 185.98 ; IR (KBr)/cm^{-1} 2932, 2854, 1666,1512, 1342, 1172; HRMS (ESI): Calcd for $C_{24}H_{18}N_2O_4$ (MH^+) 399.1346; Found 399.1342.

1-(4-methoxyphenyl)-2-(4-nitrophenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54c**)



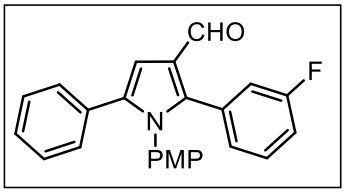
Yellow solid (M.P = 163-164 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.75 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.09-7.11 (m, 2H), 7.23 (t, *J* = 3.5 Hz, 3H), 7.37 (d, *J* = 8.6 Hz, 2H), 8.15 (d, *J* = 8.7 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.35, 108.33, 114.35 (2C), 123.18 (2C), 124.57, 127.59, 127.97 , 128.22 (2C), 128.78 (2C), 129.46 (2C), 131.81 (2C), 133.04, 133.23, 137.91, 140.19, 147.28, 159.25, 186.04; IR (KBr)/cm^{-1} 2924, 2854, 1674, 1596, 1342, 1172; HRMS (ESI): Calcd for $C_{24}H_{18}N_2O_4$ (MH^+) 399.1346; Found 399.1338.

2-(2-fluorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54d**)



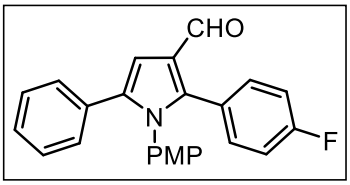
Reddish solid (M.P = 145-146 ^{0}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 6.69 (d, *J* = 8.3 Hz, 2H), 6.92 (d, *J* = 6.2 Hz, 2H), 6.97 (s, 1H), 7.01 (t, *J* =8.8 Hz, 1H) 7.12 (d, *J* = 6.7 Hz, 3H), 7.20 (bs, 4H), 7.34 (d, *J* = 5.9, 1H), 9.62 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.26, 107.29, 113.81 (2C), 115.66, 115.83, 123.78, 123.81, 124.63, 127.26,128.13 (2C),128.64 (2C), 129.10, 129.95, 131.16, 131.22, 131.58, 133.30, 137.43, 138.03, 158.90, 186.36; IR (KBr)/cm^{-1} 2932, 2854, 1659, 1250, 1180, 1026; HRMS (ESI): Calcd for $C_{24}H_{18}FNO_2$ (MH^+) 372.1401; Found 372.1409.

2-(3-fluorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54e**)



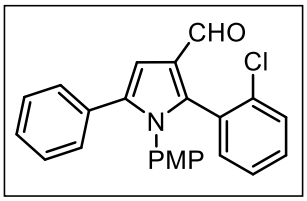
Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.88-6.91 (m, 3H), 6.96 (s, 1H), 6.99-7.05 (m, 2H), 7.09-7.11 (m, 2H), 7.20-7.24 (m, 3H), 7.42 (d, *J* = 7.3 Hz, 1H), 9.71 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.34, 107.36, 114.19 (2C), 115.45, 115.66, 118.00, 118.22, 124.18, 125.36 (2C), 127.08, 127.11, 127.34, 127.87, 128.58 (2C), 129.56, 129.64, 129.75, 137.13, 159.07, 163.30, 186.63; IR (KBr)/cm^{-1} 2908, 1680, 1247, 1174; HRMS (ESI): Calcd for $C_{24}H_{18}FNO_2$ (MH^+) 372.1401; Found 372.1395.

2-(4-fluorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54f**)



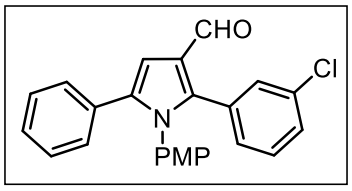
Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.95 (s, 1H), 6.99 (t, *J* = 8.7 Hz, 2H), 7.09-7.11 (m, 2H), 7.16-7.22 (m, 5H), 9.68 (s,1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.33, 107.21, 114.08 (2C), 115.17, 115.35, 124.02, 127.28, 128.14 (2C), 128.78 (2C), 129.56 (2C), 129.79, 131.58, 132.90, 132.96, 136.88, 142.96(2C), 158.93, 176.15, 186.76; IR (KBr)/cm^{-1} 2924, 2854, 1659, 1218, 1157, 1049; HRMS (ESI): Calcd for $C_{24}H_{18}FNO_2$ (MH^+) 372.1401; Found 372.1397.

2-(2-chlorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54g**)



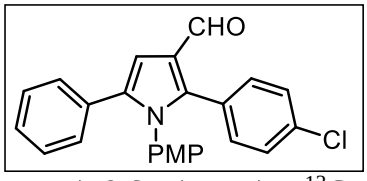
Red oily liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 6.67 (d, *J* = 9.1 Hz, 2H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.96 (s, 1H), 7.11-7.14 (m, 2H), 7.19-7.23 (m, 4H), 7.27-7.31 (m, 2H), 7.37 (d, *J* = 8.2 Hz, 1H), 9.53 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.26, 106.98, 113.80 (2C), 124.39, 126.25 (2C), 127.20 (2C), 129.11 (2C), 129.30, 129.51 (2C), 129.96, 135.53 (2C), 131.65, 133.49 (2C), 135.57, 136.96, 158.89, 186.21; IR (KBr)/cm^{-1} 2924, 2854, 1666, 1250, 1180; HRMS (ESI): Calcd for $C_{24}H_{18}ClNO_2$ (MH^+) 388.1105; Found 388.1106.

2-(3-chlorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54h**)



Brownish red oily liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 6.94 (s, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.09 (dd, *J* = 7.0 Hz, 5.9 Hz, 2H), 7.17-7.24 (m, 6H), 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 107.43, 114.18 (2C), 124.28, 127.36, 127.88 (2C), 128.16 (2C), 128.80 (2C), 129.23, 129.31, 129.57 (2C), 131.14, 131.34, 131.56, 134.00, 137.21, 143.03, 159.13 , 186.53; IR (KBr)/cm^{-1} 2932, 1666, 1250, 1165, 1034; HRMS (ESI): Calcd for $C_{24}H_{18}ClNO_2$ (MH^+) 388.1105; Found 388.1094.

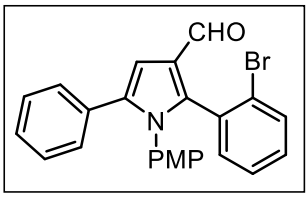
2-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54i**)



Yellow viscous oily liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.94 (s, 1H), 7.07-7.10 (m, 4H), 7.19 (t, *J* = 3.7 Hz, 3H), 7.25 (d, *J* = 5.2 Hz, 2H) 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.31, 107.42, 114.14 (2C), 124.08, 127.30, 128.12 (2C), 128.34 (2C), 128.75 (2C), 129.54 (2C), 129.72, 131.53, 132.32 (2C),

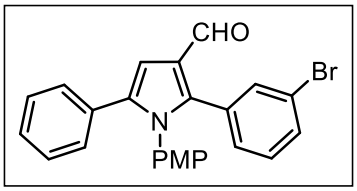
134.70, 137.08, 142.68, 152.98, 159.02, 186.55; IR (KBr)/cm^{-1} 2924, 2854, 1659, 1250, 1157, 1088; HRMS (ESI): Calcd for $C_{24}H_{18}ClNO_2$ (MH^+) 388.1105; Found 388.1103.

2-(2-bromophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54j**)



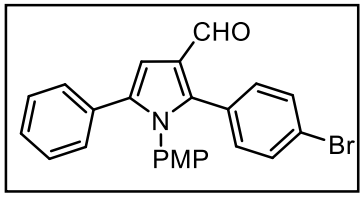
Reddish viscous oil; ^1H NMR (400 MHz, $CDCl_3$) δ 3.69 (s, 3H), 6.64 (d, *J* = 9.1 Hz, 2H), 6.93 (bs, 3H), 7.07-7.12 (m, 2H), 7.15-7.21 (m, 4H), 7.22-7.25 (m, 2H), 7.53 (d, *J* = 8.0 Hz, 1H), 9.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.22, 106.78, 113.74 (2C), 124.12, 125.89, 126.78, 127.15, 128.12 (2C), 128.48, (2C), 129.14 (2C), 129.84, 130.63, 131.32, 131.57, 132.58, 133.48, 136.74, 142.89, 158.82, 186.22; IR (KBr)/cm^{-1} 2924, 2854, 1674, 1242, 1173, 1034; HRMS (ESI): Calcd for $C_{24}H_{18}BrNO_2$ (MH^+) 432.0600; Found 432.0605.

2-(3-bromophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54k**)



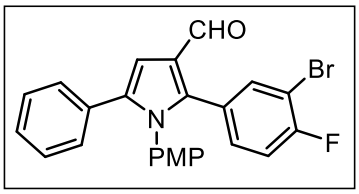
Red solid (M.P = 170-171 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.9 Hz, 2H), 7.02 (s, 1H), 7.11-7.17 (m, 5H), 7.20-7.24 (m, 4H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.11, 107.17, 113.99 (2C), 121.76, 124.05, 124.83, 127.18, 127.80, 127.97 (2C), 128.07, 128.14, 128.55 (2C), 129.31, 129.37 (2C), 129.53, 131.28, 133.74 137.01, 158.94, 186.16; IR (KBr)/cm^{-1} 2924, 2854, 1659, 1250, 1157, 1041; HRMS (ESI): Calcd for $C_{24}H_{18}BrNO_2$ (MH^+) 432.0600; Found 432.0602.

2-(4-bromophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54l**)



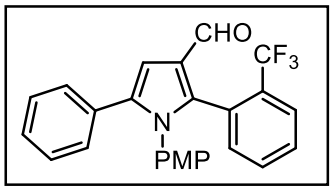
White solid (M.P = 167-168 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 6.58 (d, *J* = 8.8 Hz, 2H), 6.72 (d, *J* = 8.9 Hz, 2H), 6.80 (s, 1H), 6.90-6.95 (m, 4H), 7.06 (t, *J* = 3.6 Hz, 3H), 7.14 (t, *J* = 7.3 Hz, 1H), 7.21 (t, *J* = 7.2 Hz, 1H), 9.54 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.31, 107.42, 114.13 (2C), 124.00, 127.30, 127.83, 128.12 (2C), 128.36, 128.54 (2C), 129.51 (2C), 129.64, 131.27 (2C), 131.47, 132.55 (2C), 137.07, 142.65, 158.97, 186.57; IR (KBr)/cm^{-1} 2932, 2847, 1666, 1250, 1168, 1034; HRMS (ESI): Calcd for $C_{24}H_{18}BrNO_2$ (MH^+) 432.0600; Found 432.0595.

2-(3-bromo-4-fluorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole (**54m**)



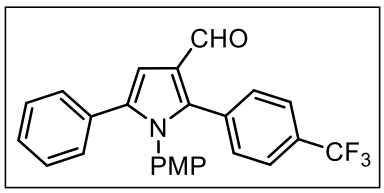
Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.76 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 6.94 (s, 1H), 7.00-7.11 (m, 4H), 7.20-7.23 (m, 3H), 7.47 (dd, *J* = 6.5 Hz, 6.6 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 107.42, 114.22 (2C), 116.06, 116.24, 124.22, 127.40, 128.17 (2C), 128.73 (2C), 129.52 (2C), 131.36, 131.65, 131.71, 136.06, 137.19, 142.94 (2C), 159.11, 176.12 , 186.30; IR (KBr)/cm^{-1} 2924, 2854, 1666, 1250, 1157, 1041; HRMS (ESI): Calcd for $C_{24}H_{17}BrFNO_2$ (MH^+) 450.0506; Found 450.0511.

1-(4-methoxyphenyl)-5-phenyl-2-(2-(trifluoromethyl)phenyl)-1*H*-pyrrole (**54n**)



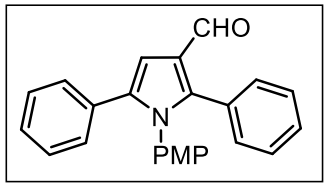
Brown viscous liquid (83 mg, 66%,); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H), 6.80 (s, 1H), 6.89 (d, *J* = 8.4 HZ, 2H), 7.06-7.12 (m, 4H), 7.17 (bs, 3H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 9.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.44. 109.36, 113.86, 114.64 (2C), 122.37, 126.97, 128.06 (2C), 128.13 (2C), 128.35 (2C), 128.56 (2C), 129.39 (2C), 129.66, 133.86, 133.15, 136.17, 136.37, 142.26, 159.63, 185.94; IR (KBr)/cm^{-1} 2970, 1681, 1512, 1442, 1373, 1249; Calcd for $C_{25}H_{18}F_3NO_2$ (MH^+) 422.1369; Found 422.1367 422.1372.

1-(4-methoxyphenyl)-5-phenyl-2-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole carbaldehyde (**54o**)



Yellow oily liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 6.71 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.9 Hz, 2H), 6.95 (s, 1H), 7.06-7.09 (m, 2H), 7.19 (t, *J* = 3.3 Hz, 3H), 7.24 (d, *J* = 6.3 Hz, 2H), 7.52 (d, *J* = 8.1 Hz, 2H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.32, 107.68, 114.20 (2C), 124.32, 124.94, 124.97, 127.41, 127.84 (2C), 128.16 (2C), 128.77(2C), 129.49 (2C), 131.37 (2C), 133.17, 137.38, 141.85, 142.94 (2C), 159.06, 186.41; IR (KBr)/cm^{-1} 2924, 2854, 1674, 1250, 1118; HRMS (ESI): Calcd for $C_{25}H_{18}F_3NO_2$ (MH^+) 422.1369; Found 422.1374.

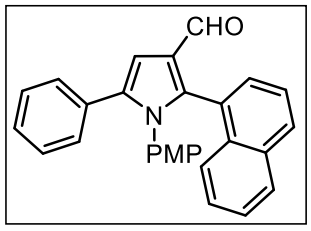
1-(4-methoxyphenyl)-2, 5-diphenyl-1*H*-pyrrole-3-carbaldehyde (**54p**)



Yellow viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 6.96 (s, 1H), 7.11 (dd, *J* = 7.4 Hz, 5.9 Hz, 2H), 7.18-7.22 (m, 5H), 7.27-7.32 (m, 3H),

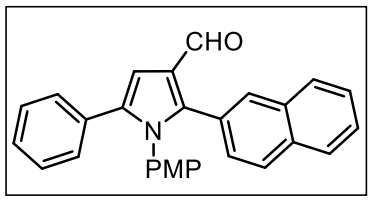
9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.32, 107.17, 114.00 (2C), 123.98, 123.37 (2C), 127.20 , 127.88,128.42, 128.59 (2C), 128.80 (2C), 129.45, 129.65 (2C), 130.06, 131.20 (2C), 131.77, 136.81, 158.89, 187.11; IR (KBr)/cm^{-1} 2924, 2854, 1666, 1242, 1165, 1034; HRMS (ESI): Calcd for $C_{24}H_{19}NO_2$ (MH^+) 354.1495; Found 354.1498.

1-(4-methoxyphenyl)-2-(naphthalen-1-yl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54q**)



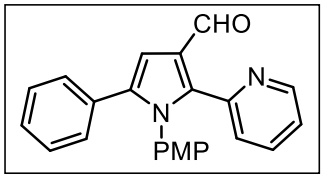
Deep red pasty liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 6.51 (d, *J* = 8.2 Hz, 2H), 6.82 (d, *J* = 7.7 Hz, 2H), 7.05 (s, 1H), 7.15-7.17 (m, 2H), 7.21-7.24 (m, 3H), 7.38-7.46 (m, 4H), 7.70 (d, *J* = 8.9 Hz, 1H), 7.81-7.85 (m, 2H), 9.39 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.16, 106.86, 113.68 (2C), 124.64, 125.34, 125.80, 126.15, 126.81, 127.16, 127.28, 128.18 (2C), 128.58 (2C), 128.87, 129.53, 130.21, 130.46, 131.82, 133.13, 133.76, 137.01, 143.11, 157.68, 157.87, 158.64, 186.79; IR (KBr)/cm^{-1} 3016, 1658, 1512, 1249, 1172; HRMS (ESI): Calcd for $C_{28}H_{21}NO_2$ (MH^+) 404.1651; Found 404.1648.

1-(4-methoxyphenyl)-2-(naphthalen-2-yl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54r**)



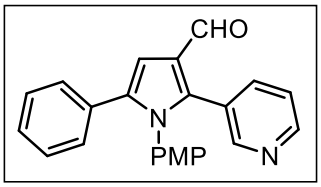
White solid (M.P = 176-177 ºC); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 6.68 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 7.01 (s, 1H), 7.12 – 7.15 (m, 3H), 7.22-7.24 (m, 3H), 7.52 (dd, *J* = 6.1 Hz, 6.1 Hz, 2H),7.68 (d, *J* = 8.5 Hz, 1H), 7.80-7.84 (m,3H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.29, 107.33, 114.07 (2C), 124.25, 126.61, 126.89, 127.24, 127.60, 127.66, 127.81, 127.88, 128.15 (2C), 128.20, 128.81 (2C), 129.60 (2C), 130.06, 131.19, 131.74, 132.60, 132.69, 136.94, 139.28, 158.86, 187.24; IR (KBr)/cm^{-1} 2922, 1668, 1248, 1172; HRMS (ESI): Calcd for $C_{28}H_{21}NO_2$ (MH^+) 404.1651; Found 404.1654.

1-(4-methoxyphenyl)-5-phenyl-2-(pyridin-2-yl)-1*H*-pyrrole-3-carbaldehyde (**54s**)



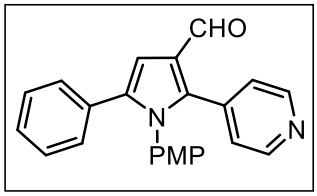
Reddish brown pasty liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.98 (s, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 7.08-7.11 (m, 2H), 7.18-7.22 (m, 4H), 7.53-7.57 (m, 1H), 8.61-8.62 (m, 1H), 9.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.33, 107.78, 114.00 (2C), 122.60, 125.10, 126.10, 127.30, 128.11 (2C), 128.89 (2C), 129.51 (2C), 130.19, 131.64, 135.73, 137.23, 141.75, 149.24, 149.53, 158.97, 187.58; IR (KBr)/cm^{-1} 2932, 1659, 1250, 1173; HRMS (ESI): Calcd for $C_{23}H_{18}N_2O_2$ (MH^+) 355.1447; Found 355.1442.

1-(4-methoxyphenyl)-5-phenyl-2-(pyridin-3-yl)-1*H*-pyrrole-3-carbaldehyde (**54t**)



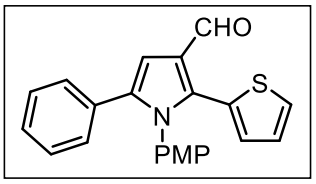
Reddish brown pasty liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 9.0 Hz, 2H), 6.99 (s, 1H), 7.10-7.12 (m, 2H), 7.22 (t, *J* = 3.3 Hz, 4H),7.49-7.52 (m, 1H), 8.49 (s, 1H),8.55 (d, *J* = 3.9 Hz, 1H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.33, 107.83, 114.31 (2C), 122.90, 124.69, 126.06, 127.47, 128.18 (2C), 128.77 (2C), 129.35, 129.63 (2C), 131.33, 137.71, 138.39, 139.72, 149.08, 150.93, 159.22, 186.12; IR (KBr)/cm^{-1} 2932, 1666, 1250, 1180, 1026; HRMS (ESI): Calcd for $C_{23}H_{18}N_2O_2$ (MH^+) 355.1447; Found 355.1448.

1-(4-methoxyphenyl)-5-phenyl-2-(pyridin-4-yl)-1*H*-pyrrole-3-carbaldehyde (**54u**)



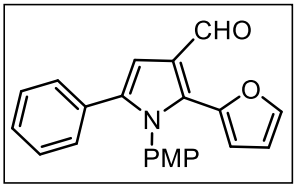
Yellow pasty liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.76 (s, 3H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.97 (s, 1H), 7.07-7.09 (m, 4H), 7.21 (t, *J* = 3.1 Hz, 3H), 8.55 (s, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.31, 108.03, 114.25 (2C), 124.41, 125.41, 127.50 (2C), 128.18 (2C), 128.73 (2C), 129.24, 129.38 (2C), 131.08, 137.57, 137.83, 139.88, 149.32 (2C), 159.19, 186.07; IR (KBr)/cm^{-1} 2931, 1674, 1250, 1173, 1026; HRMS (ESI): Calcd for $C_{23}H_{18}N_2O_2$ (MH^+) 355.1447; Found 355.1444.

1-(4-methoxyphenyl)-5-phenyl-2-(thiophen-2-yl)-1*H*-pyrrole-3-carbaldehyde (**54v**)



Yellowish orange pasty liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.96-7.00 (m, 5H),7.11-7.13 (m, 2H), 7.21 (t, *J* = 3.7 Hz, 4H), 9.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.36, 107.40, 114.08 (2C), 121.88, 125.36 (2C), 126.81, 127.38, 127.88 (2C), 128.55, 128.59 (2C), 128.73 (2C), 129.87 (2C), 130.81, 132.99, 159.38, 186.90; IR (KBr)/cm^{-1} 2924, 2854, 1666, 1242, 1173 1034; Found 356.0295. HRMS (ESI): Calcd for $C_{22}H_{17}NO_2S$ (MH^+) 360.1059; Found 360.1064.

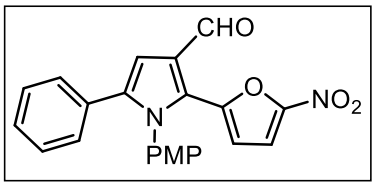
2-(furan-2-yl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54w**)



Blood red liquid (52 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 3H) , 6.80 (s, 1H), , 6.89 (d, *J* = 8.8 Hz, 2H) , 7.07 (dd, *J* = 7.3, 2.2 Hz, 2H) , 7.11 (d, *J* = 8.8 Hz, 2H) , 7.17 (d, *J* = 1.4 Hz, 1H) , 7.41 (t, *J* = 7.5 Hz, 2H) , 7.54 (t, *J* = 7.4 Hz, 1H) , 7.84 (d, *J* = 7.4 Hz, 2H), 9.99 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ; 55.41, 109.31, 114.61 (2C), 122.30, 125.95, 126.95,

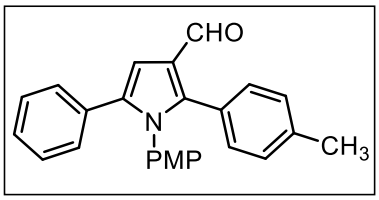
128.03 (2C), 128.10 (2C), 128.31, 128.54, 129.35, 129.59, 131.78, 133.15, 136.16, 136.28, 142.33, 159.58, 185.96; IR (KBr)/cm^{-1} 2970, 1682, 1582, 1466, 1265, 1011 HRMS (ESI): Calcd for $C_{22}H_{17}NO_3$ (MH^+) 344.1279; Found 344.1286.

1-(4-methoxyphenyl)-2-(5-nitrofuran-2-yl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54x**)



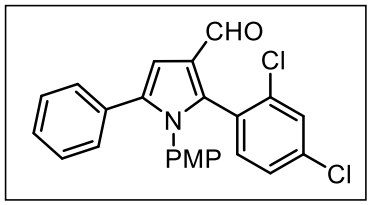
Blood red pasty liquid (82 mg, 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 6.96 (d, *J* = 8.9 Hz, 2H), 7.02 (s, 1H), 7.06-7.08 (m, 2H), 7.34 (d, *J* = 8.9 Hz, 2H), 7.42 (t, *J* = 7.8 Hz, 2H), 7.53 (d, *J* = 7.3 Hz, 1H), 7.85 (d, *J* = 7.3 Hz, 2H), 10.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ ^{13}C NMR (101 MHz, $CDCl_3$) δ 55.53, 109.54 , 112.70 , 114.69 (2C), 122.39, 126.85, 128.30 (2C), 128.55, 128.80 (2C), 129.36, 129.64 (2C), 129.94, 130.56, 133.16, 139.99, 147.35, 160.17, 186.38; IR (KBr)/cm^{-1} 3939, 1666, 1512, 1350, 1250, 1180; HRMS (ESI): Calcd for $C_{22}H_{16}N_2O_5$ (MH^+) 389.1138; Found 389.1144.

1-(4-methoxyphenyl)-5-phenyl-2-(p-tolyl)-1*H*-pyrrole-3-carbaldehyde (**54y**)



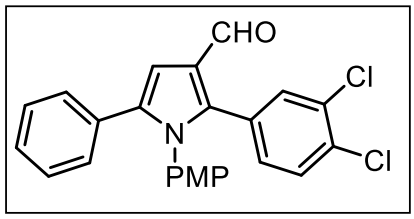
Brown pasty liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.33 (s, 3H), 3.76 (s, 3H), 6.72 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 6.95 (s, 1H), 7.08 (bs, 5H), 7.20 (bs, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 9.69 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.67, 55.34, 107.09, 113.97 (2C), 123.88, 125.34, 126.41, 127.12, 127.86, 128.08, 128.57, 128.75(2C), 129.62, 130.16, 131.03 (2C), 131.84, 136.69, 138.36, 143.00, 144.79, 158.84, 187.16 ; IR (KBr)/cm^{-1} 2914, 1668, 1248, 1178; HRMS (ESI): Calcd for $C_{25}H_{21}NO_2$ (MH^+) 368.1651; Found 368.1648.

2-(2, 4-dichlorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54z**)



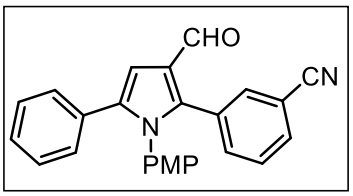
Yellow liquid (73 mg, 57 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.70 (d, *J* = 9.0 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 6.95 (s, 1H), 7.11-7.13 (m, 3H), 7.20-7.22 (m, 5H),), 9.55 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.17, 107.14, 113.36 (2C), 124.37,124.97, 126.71, 127.24, 128.10 (2C), 129.94 (2C), 129.36 (2C), 129.52, 131.31, 133.15, 134.02 (2C), 135.78, 136.19, 137.11, 139.42, 158.90, 185.77; IR (KBr)/cm^{-1} 2926, 1688, 1514, 1249, 1161; HRMS (ESI): Calcd for $C_{24}H_{17}Cl_2NO_2$ (MH^+) 422.0705; Found 422.0711.

2-(3,4-dichlorophenyl)-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (**54aa**)



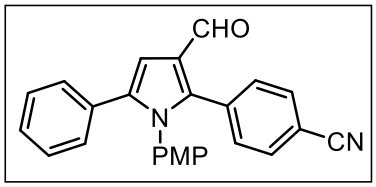
Reddish brown liquid (70 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s,3H), 6.76 (d, *J* = 8.8 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 6.95 (s, 1H), 6.97 (d, *J* = 2.0 Hz, 1H), 6.99 (d, *J* = 2.0 Hz, 1H), 7.08-7.11 (m, 2H), 7.22 (t, *J* = 3.3 Hz, 4H), 9.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.29, 107.54, 114.21 (2C), 124.18, 127.38, 127.92, 128.12 (2C), 128.67 (2C), 129.42 (2C), 129.30, 129.97, 130.11, 131.23, 132.24, 132.69, 132.85, 137.31, 140.78, 159.08, 186.13; IR (KBr)/cm^{-1} 2958, 2839, 1680, 1516, 1446, 1219, 1159 ; HRMS (ESI): Calcd for $C_{24}H_{17}Cl_2NO_2$ (MH^+) 422.0705; Found 422.0711.

3-(3-formyl-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrol-2-yl)benzonitrile (**54ab**)



Yellow oily liquid (74 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s,3H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.96 (s, 1H), 7.09-7.11 (m, 2H), 7.22 (t, *J* = 3.3 Hz, 3H), 7.40-7.48 (m, 3H), 7.60 (d, *J* = 7.3 Hz, 1H), 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.33, 107.85, 112.42, 114.29 (2C), 118.00, 124.36, 127.48, 128.17 (2C), 128.73 (2C), 128.94, 129.20, 129.48 (2C), 131.09, 131.21, 131.83, 134.22, 135.27, 137.50, 140.44, 159.19, 185.93 ; IR (KBr)/cm^{-1} 2932, 2230, 1659, 1512, 1443, 1250; HRMS (ESI): Calcd for $C_{25}H_{18}N_2O_2$ (MH^+) 379.1479; Found 379.1473.

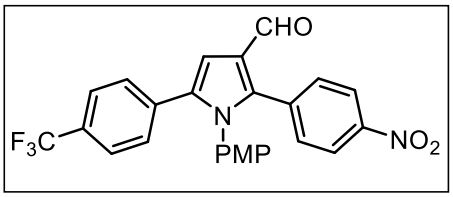
4-(3-formyl-1-(4-methoxyphenyl)-5-phenyl-1*H*-pyrrol-2-yl)benzonitrile (**54ac**)



Pink pasty liquid (78 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.97 (s, 1H), 7.09 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.20-7.24 (m, 3H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H), 9.72 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.37 , 108.19 , 112.09 , 114.32 (2C), 118.25, 124.45 , 127.08 , 127.56 , 128.21 (2C), 128.81 (2C), 129.50 (2C), 131.24, 131.63 (2C), 131.70 (2C), 134.34, 137.75, 140.74, 159.26, 186.05; IR (KBr)/cm^{-1} 2923, 2225, 1674, 1512, 1450, 1249, 1172; HRMS (ESI): Calcd for $C_{25}H_{18}N_2O_2$ (MH^+) 379.1479; Found379.1483.

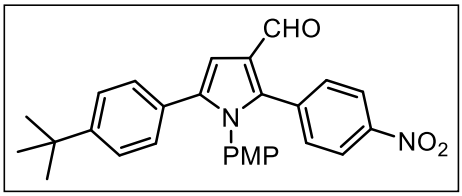
4.8 Analytical data of synthesized compounds (55a-55ak)

1-(4-methoxyphenyl)-2-(4-nitrophenyl)-5-(4-(trifluoromethyl)phenyl)-1*H*-pyrrole (55a)



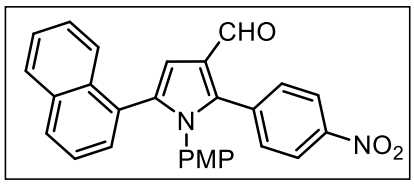
Yellow pasty liquid (90 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.07 (s, 1H), 7.36-7.42 (m, 4H), 7.59 (d, *J* = 8.2 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.42, 109.47, 114.65 (2C), 122.60, 123.39 (2C), 124.77,127.03, 128.00, 128.73 (2C), 129.41 (2C), 130.18, 130.45 (2C), 130.70 (2C), 131.85 (2C), 146.07 (2C), 159.57, 185.87; IR (KBr)/cm^{-1} 2933, 1724, 1660, 1249, 1174; HRMS (ESI): Calcd for $C_{25}H_{17}F_3N_2O_4$ (MH^+) 467.1219; Found 467.1225.

5-(4-(tert-butyl) phenyl)-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole (55b)



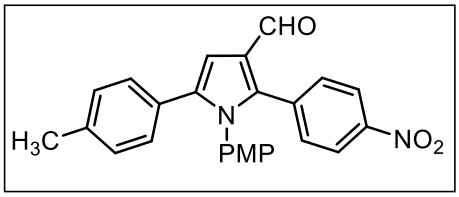
Brownish pasty liquid (89 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28, (s, 9H), 3.78 (s, 3H), 6.76 (d, *J* = 8.9 Hz, 2H), 6.91 (d, *J* = 8.8 Hz, 2H), 6.96 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.34 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 8.8 Hz, 2H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.15 (3C), 34.50, 55.36, 108.01, 114.32 (2C), 123.14 (2C), 123.84, 123.90, 124.57, 125.18 (2C), 126.70, 127.01, 127.72 , 128.27 (2C), 129.53 (2C), 131.82 (2C), 147.22, 150.59, 159.22, 186.06; IR (KBr)/cm^{-1} 2932, 2862, 1666, 1250, 1180, 1026; HRMS (ESI): Calcd for $C_{28}H_{26}N_2O_4$ (MH^+) 455.1972; Found 455.1976.

1-(4-methoxyphenyl)-5-(naphthalen-1-yl)-2-(4-nitrophenyl)-1*H*-pyrrole (55c)



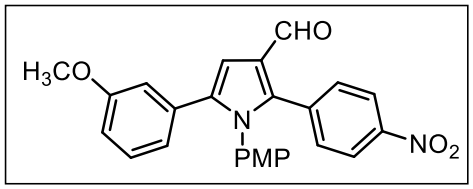
Yellow viscous liquid (74 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 6.52 (d, *J* = 8.7 Hz, 2H), 6.76 (d, *J* = 8.2 Hz, 2H), 7.04 (s, 1H), 7.20-7.24 (m, 2H), 7.78-7.87 (m, 4H), 7.90-7.98 (m, 3H), 8.16 (d, *J* = 8.8 Hz, 2H), 9.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.19, 110.57, 113.98 (2C), 123.27 (2C), 124.72, 125.66, 125.92 , 126.04, 126.50,128.24, 128.99 (2C), 129.27,129.49, 130.00, 131.78 (2C), 132.87, 133.40, 135.88, 136.37, 139.51, 137.36, 158.96, 186.11; IR (KBr)/cm^{-1} 2924, 2854, 1674, 1234, 1180; HRMS (ESI): Calcd for $C_{28}H_{20}N_2O_4$ (MH^+) 449.1502; Found 449.1508.

1-(4-methoxyphenyl)-2-(4-nitrophenyl)-5-(p-tolyl)-1*H*-pyrrole-3-carbaldehyde (55d)



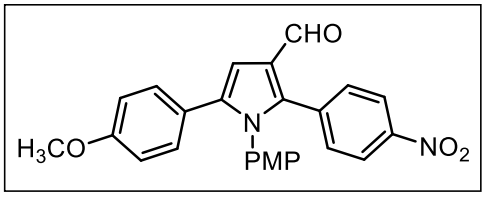
Yellow solid, (M.P = 156-157 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.77 (s,3H), 6.75 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 1H), 6.98 (d, *J* = 8.1 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.6 Hz, 2H), 8.14 (d, J= 8.7 Hz, 2H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.15, 55.37, 107.98, 114.34 (2C), 123.19 (2C), 124.55, 128.12, 128.67 (2C), 128.98 (2C), 129.49 (2C), 130.17, 131.82 (2C), 136.26, 137.53, 138.08, 140.08, 147.27, 159.22, 186.14; IR (KBr)/cm^{-1} 2936, 2862, 1782, 1234; HRMS (ESI): Calcd for $C_{25}H_{20}N_2O_4$ (MH^+) 413.1502; Found 413.1505.

5-(3-methoxyphenyl)-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole (55e)



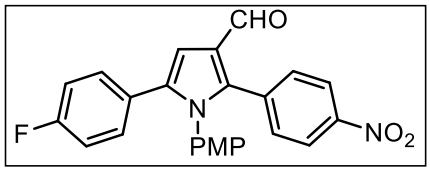
Yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.65 (s, 3H), 3.77 (s, 3H), 6.64-6.69 (m, 2H), 6.75-6.79 (m, 3H), 6.90 (d, *J* = 8.9 Hz, 2H), 7.00 (s, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.8 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.09, 55.43, 108.50, 113.70, 114.08, 114.42 (2C), 121.28, 123.21 (2C), 124.63, 129.27, 129.44, 129.50 (2C), 131.86 (2C), 132.40, 136.24, 137.80, 140.29, 147.40, 159.26, 159.39, 186.00; IR (KBr)/cm^{-1} 2962, 2823, 1666, 1519, 1342, 1234; HRMS (ESI): Calcd for $C_{25}H_{20}N_2O_5$ (MH^+) 429.1451; Found 429.1454.

1, 5-bis (4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole-3-carbaldehyde (55f)



Yellow solid (M.P = 145-146 ^{o}C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 6H), 6.75 (dd, *J* = 8.3 Hz, 8.6 Hz, 4H), 6.86 (s, 1H), 6.90 (d, *J* = 11.0 Hz, 2H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.35 (d, *J* = 8.6 Hz, 2H), 8.14 (d, *J* = 8.6 Hz, 2H), 9.74 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.36, 55.37, 107.60, 113.69 (2C), 114.34 (2C), 123.18 (2C), 124.54, 126.78, 129.38 , 129.52 (2C), 130.12 (2C), 131.82 (2C), 136.29, 137.91, 139.88, 147.25, 159.06, 159.21, 186.10; IR (KBr)/cm^{-1} 2924, 2854, 1776, 1250, 1165, 1034; HRMS (ESI): Calcd for $C_{25}H_{20}N_2O_5$ (MH^+) 429.1451; Found 429.1452.

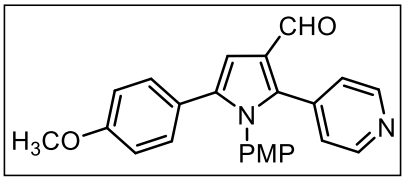
5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-1*H*-pyrrole (55g)



Yellowish oily liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.75 (d, *J* = 8.9 Hz, 2H), 6.86-6.90 (m, 3H), 7.05-7.14 (m, 4H), 7.36 (d, *J* = 8.8 Hz, 2H), 8.15 (d, *J* = 8.8 Hz,

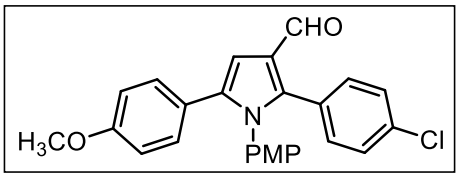
2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.40, 107.34, 113.47 (2C), 114.29, 114.46, 122.25 (2C), 128.09, 128.48 (2C), 128.60, 129.44, 129.51, 129.58, 129.63, 130.51, 131.82 (2C), 135.11, 135.60, 135.94, 158.37, 185.00; IR (KBr)/cm^{-1} 2962, 2885, 1782, 1342, 1172; HRMS (ESI): Calcd for $C_{24}H_{17}FN_2O_4$ (MH^+) 417.1251; Found 417.1257.

5-(4-methoxyphenyl)-1-(4-methoxyphenyl)-2-(pyridin-4-yl)-1*H*-pyrrole (**5h**)



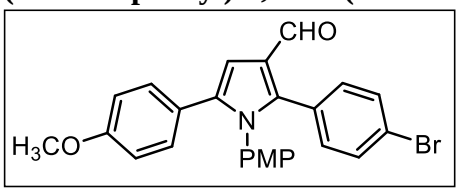
Yellow pasty liquid (62 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s,3H), 3.77 (s,3H), 6.74-6.76 (m, 4H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.91 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.08 (d, *J* = 6.0 Hz, 2H), 8.53 (d, *J* = 5.8 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.22, 55.34, 107.37, 107.44, 113.69 (2C), 114.32 (2C), 123.63, 124.47, 125.42, 125.48, 129.44, 129.50, 130.12, 130.17, 137.76, 137.90, 139.59, 149.34, 149.37, 159.05, 159.24, 187.17; IR (KBr)/cm^{-1} 2924, 1680, 1508, 1456, 1249, 1178; HRMS (ESI): Calcd for $C_{24}H_{20}N_2O_3$ (MH^+) 385.1553; Found 385.1260.

2-(4-chlorophenyl)-1, 5-bis(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (**55i**)



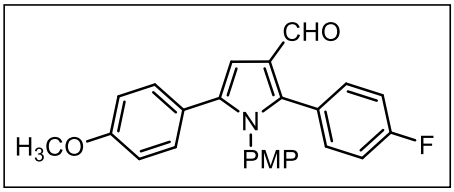
Yellow liquid (78 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (s,3H), 3.69 (s,3H), 6.64-6.67 (m, 4H), 6.78 (d, *J* = 9.2 Hz, 3H), 6.83-6.89 (m, 1H), 6.93 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.5 Hz, 2H), 7.86-7.93 (m, 1H), 9.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.16, 55.34, 106.65, 113.62 (2C), 114.14 (2C), 124.05, 1128.33 (2C), 129.11, 129.61 (2C), 130.09 (2C), 130.28, 130.44, 130.68, 132.34 (2C), 134.65, 137.02, 142.37, 158.97, 158.89, 186.59; IR (KBr)/cm^{-1} 2954, 1668, 1514, 1251, 1176; HRMS (ESI): Calcd for $C_{25}H_{20}ClNO_3$ (MH^+) 418.1211; Found 418.1217.

2-(4-bromophenyl)-1, 5-bis(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (**55j**)



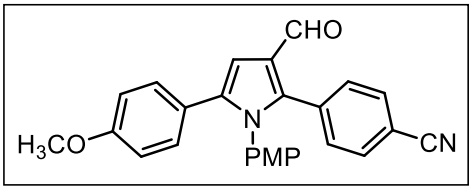
Brown liquid (91 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s,3H), 3.78 (s,3H), 6.73-6.76 (m, 4H), 6.87 (d, *J* = 9.2 Hz, 3H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.17, 55.35, 106.67, 113.61 (2C), 113.72, 114.15 (2C), 122.95, 123.97, 124.01, 128.49, 129.60 (2C), 129.78, 130.09 (2C), 130.29, 131.29 (2C), 132.59 (2C), 137.04, 158.87, 186.64; IR (KBr)/cm^{-1} 2951, 1668, 1506, 1456, 1220, 1161; HRMS (ESI): Calcd for $C_{25}H_{20}BrNO_3$ (MH^+) 462.0706; Found 462.0711.

2-(4-fluorophenyl)-1, 5-bis(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (**55k**)



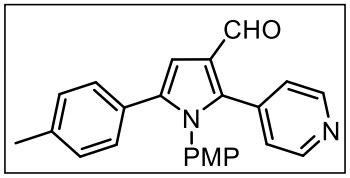
Red liquid (73 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 6H), 6.73 (d, *J* = 8.7 Hz, 3H), 6.93-6.96 (m, 2H), 6.99 (d, *J* = 9.0 Hz, 4H), 7.15-7.18 (m, 2H), 7.27 (d, *J* = 8.9 Hz, 2H), 9.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.15, 55.32, 106.38, 113.58 (2C), 114.05 (2C), 115.13, 115.30, 123.92, 124.07, 126.78, 129.60 (2C), 130.06 (2C), 130.69, 131.26, 131.33, 132.89, 132.95, 136.79. 158.80, 158.86, 186.76; (KBr)/cm^{-1} 2954, 1666, 1506, 1435, 1249, 1178; HRMS (ESI): Calcd for $C_{25}H_{20}FNO_3$ (MH^+) 402.1506; Found 402.1512.

4-(3-formyl-1, 5-bis(4-methoxyphenyl)-1*H*-pyrrol-2-yl) benzonitrile (**55l**)



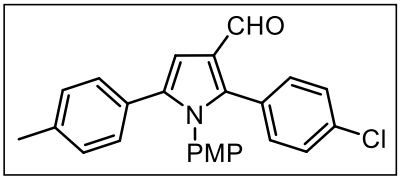
Brownish liquid (83 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s,3H), 3.78 (s,3H), 6.73-6.77 (m, 4H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.90 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 7.29 (d, *J* = 8.5 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.16, 55.36, 112.92, 113.65 (2C), 113.76, 114.05,114.27, 118.32, 123.60, 124.30, 126.77, 126.93, 129.50 (2C), 130.10 (2C), 131.60 (2C), 134.70 (2C), 137.67, 140.50, 158.99, 159.13, 186.19; IR (KBr)/cm^{-1} 2962, 2225, 1656, 1508, 1435, 1300, 1251, 1180; HRMS (ESI): Calcd for $C_{26}H_{20}N_2O_3$ (MH^+) 409.1553; Found 409.1558.

1-(4-methoxyphenyl)-2-(pyridin-4-yl)-5-p-tolyl-1*H*-pyrrole-3-carbaldehyde (**55m**)



Red pasty liquid (63 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.77 (s, 3H), 6.75 (d, *J*=8.8Hz, 2H), 6.89 (d, *J* = 8.0 Hz, 2H), 6.94 (s, 1H), 6.97 (d, *J* = 8.1 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 5.9 Hz, 2H), 8.52 (d, *J* = 5.8 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.12, 55.34, 107.69, 114.26 (2C), 124.44 (2C), 125.41 (2C), 128.21, 128.65 (2C), 128.92 (2C), 129.39, 129.44 (2C), 137.43, 137.65, 138.00, 139.78, 149.36, 159.19, 186.15; IR (KBr)/cm^{-1} 2960, 1658, 1597, 1435, 1298, 1251, 1190; HRMS (ESI): Calcd for $C_{24}H_{20}N_2O_2$ (MH^+) 369.1604; Found 369.1610.

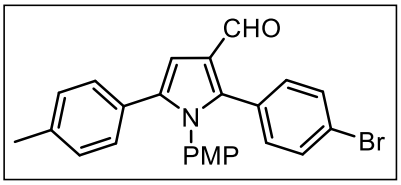
2-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-p-tolyl-1*H*-pyrrole-3-carbaldehyde (**55n**)



Reddish oily liquid (74 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.85 (s, 3H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 7.03 (s, 1H), 7.09 (d, *J* = 8.2 Hz, 2H),

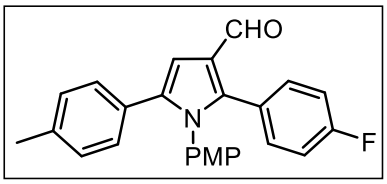
7.13 (d, *J* = 8.2 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 4H), 9.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.93, 55.28, 106.95, 114.07 (2C), 123.97, 127.94, 128.08. 128.29 (2C), 128.42, 128.59 (2C), 128.85 (2C), 129.34, 129.52 (2C), 129.74, 130.38, 134.60, 137.52, 142.55, 158.91, 186.59; IR (KBr)/cm^{-1} 2951, 1668, 1514, 1456, 1435, 1296, 1220, 1163; HRMS (ESI): Calcd for $C_{25}H_{20}ClNO_2$ (MH^+) 402.1261; Found 369.1267.

2-(4-bromophenyl)-1-(4-methoxyphenyl)-5-p-tolyl-1*H*-pyrrole-3-carbaldehyde (**55o**)



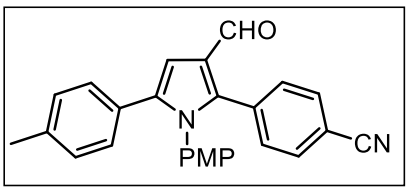
Reddish oily liquid (88 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.78 (s, 3H), 6.74 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.91 (s, 1H), 6.97 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.97, 55.31, 107.02, 114.11 (2C), 122.94, 123.97, 128.11, 128.43, 128.57, 128.62 (2C), 128.87 (2C), 129.54 (2C), 129.75, 130.57, 131.26, 132.06, 132.57, 137.55, 140.20, 158.93, 186.62; IR (KBr)/cm^{-1} 2954, 1688, 1514, 1435, 1294, 1249, 1178; HRMS (ESI): Calcd for $C_{25}H_{20}BrNO_2$ (MH^+) 446.0756; Found 446.0761.

2-(4-fluorophenyl)-1-(4-methoxyphenyl)-5-p-tolyl-1*H*-pyrrole-3-carbaldehyde (**55p**)



Yellowish liquid (78 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 3.77 (s, 3H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.87 (d, *J* = 9.0 Hz, 2H), 6.91 (s, 1H), 6.99 (d, *J* = 3.3 Hz, 2H), 7.01 (d, *J* = 2.5 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.8 Hz, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.96, 55.30, 106.77, 114.03 (2C), 115.12, 115.29, 123.96, 128.10 (2C), 128.46, 128.60 (2C), 128.86 (2C), 129.36, 129.42, 129.56 (2C), 132.88, 132.94, 137.55, 140.20, 158.87, 186.74; IR (KBr)/cm^{-1} 2951,1668, 1456, 1294, 1220, 1163; HRMS (ESI): Calcd for $C_{25}H_{20}FNO_2$ (MH^+) 386.1557; Found 386.1563.

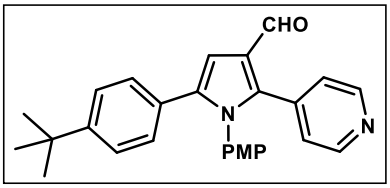
4-(3-formyl-1-(4-methoxyphenyl)-5-p-tolyl-1*H*-pyrrol-2-yl)benzonitrile (**55q**)



Yellow solid (M.P =166-167 ºC, 81 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.78 (s, 3H), 6.74 (d, *J* = 8.9Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.94 (s, 1H), 6.97 (d, *J* = 8.2 Hz, 2H), 7.03 (d, *J* = 8.1 Hz, 2H), 7.29 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.08, 55.33, 107.74, 114.25 (2C), 124.35, 128.08, 128.17, 128.41, 128.64 (2C), 128.81, 128.91 (2C), 129.19, 129.24,

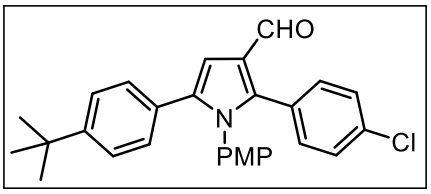
129.48 (2C), 134.34, 137.41, 137.84, 140.62, 159.17, 186.08; IR (KBr)/cm^{-1} 2966, 2222, 1680, 1514, 1433, 1251, 1178; HRMS (ESI): Calcd for $C_{26}H_{20}N_2O_2$ (MH^+) 393.1604; Found 393.1609.

5-(4-*tert*-butylphenyl)-1-(4-methoxyphenyl)-2-(pyridin-4-yl)-1*H*-pyrrole (**55r**)



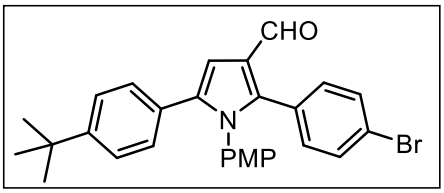
Yellowish pasty liquid (77 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 3.77 (s, 3H), 6.75 (d, *J*=8.9Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.95 (s, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.08 (d, *J* = 6.0 Hz, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 8.51 (d, *J* = 5.5 Hz, 2H), 9.73 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.12 (3C), 34.45, 55.33, 107.77 (2C), 114.25 (2C), 124.47 (2C), 125.11 (2C), 125.41 (2C), 128.12, 128.26 (2C), 129.48 (2C), 137.70, 137.93, 137.79, 149.28 (2C), 150.50, 159.22, 186.05; IR (KBr)/cm^{-1} 2960, 1658, 1597, 1512, 1435, 1296, 1251, 1190; HRMS (ESI): Calcd for $C_{27}H_{26}N_2O_2$ (MH^+) 411.2073; Found 411.2080.

5-(4-*tert*-butylphenyl)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (**55s**)



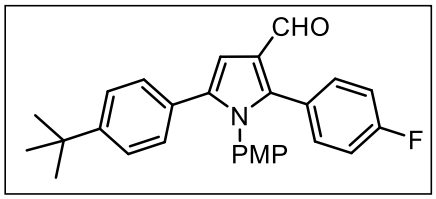
Yellow solid (M.P = 172-173 ^{o}C, 84 mg, 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 3.77 (s, 3H), 6.74 (d, *J*= 8.8Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 6.92 (s, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 4.2 Hz, 2H), 9.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.20 (3C), 34.50, 55.37, 93.94, 114.13 (2C), 124.11, 125.10 (2C), 128.07, 128.27 (2C), 128.32 (2C), 128.54, 128.64 (2C), 129.94, 132.37 (2C), 134.65, 137.15, 142.61, 150.29, 159.01, 186.60; IR (KBr)/cm^{-1} 2960, 1672, 1512, 1406, 1296, 1172; HRMS (ESI): Calcd for $C_{28}H_{26}ClNO_2$ (MH^+) 444.1731; Found 444.1736.

2-(4-bromophenyl)-5-(4-*tert*-butylphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (**55t**)



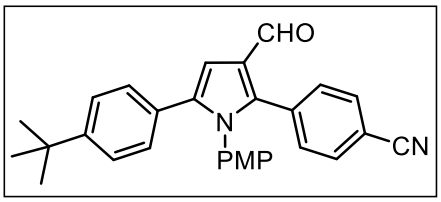
Brownish red solid (M.P =164-165 ^{o}C, 96 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 3.78 (s, 3H), 6.75 (d, *J*=8.8Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 6.94 (s, 1H), 7.02 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.42 (d, *J* = 8.4 Hz, 2H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.18 (3C), 34.47, 55.34, 107.14, 114.13 (2C), 122.93, 124.06, 125.09 (2C), 125.39, 128.25 (2C), 128.51, 129.62 (2C), 129.89, 131.25 (2C), 137.07, 132.60 (2c), 136.16, 150.27, 158.99, 186.56; IR (KBr)/cm^{-1} 2926, 1674, 1512, 1436, 1251,1192; HRMS (ESI): Calcd for $C_{28}H_{26}BrNO_2$ (MH^+) 488.1226; Found 488.1230.

5-(4-*tert*-butylphenyl)-2-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (55u)



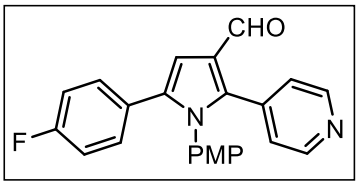
White solid (M.P = 152-153 ^{o}C, 84 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 3.77 (s, 3H), 6.74 (d, *J*= 8.9Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.93 (s, 1H), 6.96-7.03 (m, 4H), 7.15-7.19 (m, 2H), 7.22 (d, *J* = 8.4 Hz, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.18 (3C), 34.47, 55.33, 106.83, 114.04 (2C), 115.11, 115.28, 124.00, 125.08 (2C), 128.22 (2C), 128.56, 129.62 (2C), 129.95, 132.90, 132.97, 136.91, 143.10, 150.19, 158.88, 161.61, 163.59, 186.73; IR (KBr)/cm^{-1} 2958, 1672, 1512, 1363, 1253, 1172; HRMS (ESI): Calcd for $C_{28}H_{26}FNO_2$ (MH^+) 428.2027; Found 428.2032.

4-(5-(4-*tert*-butylphenyl)-3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)benzonitrile(55v)



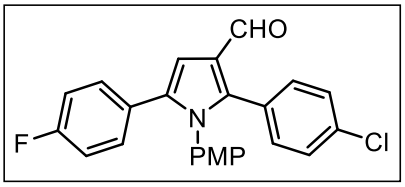
Yellow solid (M.P = 160-161 ^{o}C, 91 mg, 69%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 3.79 (s, 3H), 6.75 (d, *J*= 8.9Hz, 2H), 6.89 (d, *J* = 8.8 Hz, 2H), 6.95 (s, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.3 Hz, 2H), 7.57 (d, *J* = 8.3 Hz, 2H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.18 (3C), 34.52, 55.40, 107.88 (2C), 122.00, 114.29 (2C), 118.31, 124.44, 125.18 (2C), 128.21, 128.32 (2C), 129.57 (2C), 131.65 (2C), 131.68 (2C), 134.42, 137.81, 140.68, 150.58, 159.23, 186.12; IR (KBr)/cm^{-1} 2954, 2225, 1682, 1514, 1433, 1249, 1178; HRMS (ESI): Calcd for $C_{29}H_{26}N_2O_2$ (MH^+) 435.2073; Found 435.2079.

5-(4-fluorophenyl)-1-(4-methoxyphenyl)-2-(pyridin-4-yl)-1*H*-pyrrole-3-carbaldehyde (55w)



Yellowish viscous liquid (69 mg, 58%); ^{1}H NMR (400 MHz, $CDCl_3$) 3.77 (s, 3H), 6.75 (d, *J*=8.9Hz, 2H), 6.86-6.93 (m, 5H), 7.03-7.09 (m, 4H),8.53 (d, *J* = 5.9 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.37, 108.01, 114.37 (2C), 115.21, 115.39, 124.41, 125.36 (2C), 129.07, 129.41 (2C), 130.54, 130.60, 136.86, 137.47, 139.92, 149.46(2C), 159.31, 161.14, 163.12, 186.05; IR (KBr)/cm^{-1}2970, 1674, 1514, 1436, 1298, 1257, 1155; HRMS (ESI): Calcd for $C_{23}H_{17}N_2O_2$ (MH^+) 373.1353; Found 373.1349.

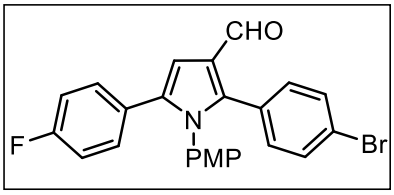
2-(4-chlorophenyl)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (55x)



Brown pasty liquid (71 mg, 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.84- 6.93 (m, 4H), 7.02-7.07 (m, 3H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.34-

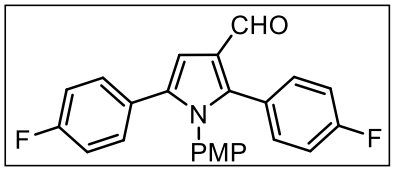
7.38 (m, 2H), 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 107.41, 114.26 (2C), 115.14, 115.36, 115.51, 115.72, 124.08, 127.21, 127.29, 127.89, 128.42 (2C), 129.58 (2C) 130.52, 130.60, 132.33 (2C), 134.83, 136.10, 159.17, 186.52; IR (KBr)/cm^{-1} 2956, 1687, 1504, 1415, 1294, 1224, 1159; HRMS (ESI): Calcd for $C_{24}H_{17}FClNO_2$ (MH^+) 406.1011; Found 406.1016.

2-(4-bromophenyl)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (**55y**)



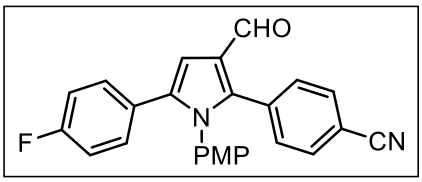
Red pasty liquid (85 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.83- 6.93 (m, 5H), 7.01-7.07 (m, 4H), 7.43 (d, *J* = 8.5 Hz, 2H), 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 107.41, 114.26 (2C), 115.14, 115.36, 115.51, 115.72, 124.08, 127.21, 127.29, 127.89, 128.42 (2C), 129.58 (2C) 130.52, 130.60, 132.33 (2C), 134.83, 136.10, 159.17, 186.52; IR (KBr)/cm^{-1} 2954, 1688, 1600, 1506, 1224, 1157; HRMS (ESI): Calcd for $C_{24}H_{17}BrFNO_2$ (MH^+) 450.0456; Found 450.0450.

2, 5-bis(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-3-carbaldehyde (**55z**)



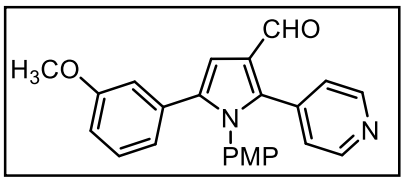
Brown pasty liquid (72 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.73 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.91 (t, *J* = 9.0 Hz, 8.4 Hz 3H), 7.12-7.19 (m, 4H), 7.99-8.08 (m, 2H), 9.67 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.34, 107.17, 114.17 (2C), 115.10, 115.17, 115.31, 124.02, 129.58 (2C), 130.48, 130.56, 132.88, 132.96, 135.90,138.67 (2C), 138.70 (2C), 158.07, 161.03, 163.49, 186.59; IR (KBr)/cm^{-1} 2959, 1670,1504, 1415, 1294, 1224, 1159; HRMS (ESI): Calcd for $C_{24}H_{17}F_2NO_2$ (MH^+) 390.1306; Found 390.1309.

4-(5-(4-fluorophenyl)-3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrol-2 yl)benzonitrile (**55aa**)



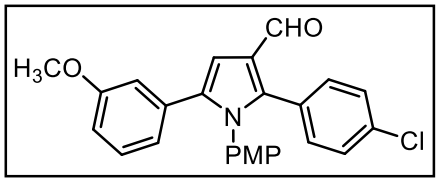
Red pasty liquid (72 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 6.75 (d, *J*= 8.9Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.90-6.95 (m, 3H), 7.04-7.07 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz 2H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 108.05, 112.11, 114.38 (2C), 115.29, 115.41, 118.25, 124.33, 127.34, 129.10, 129.45 (2C), 130.54, 130.61, 131.59 (2C), 131.76 (2C), 134.15, 136.70, 140.76, 159.27, 161.17, 186.05; IR (KBr)/cm^{-1} 2956, 2227, 1666, 1598, 1514, 1226, 1157; HRMS (ESI): Calcd for $C_{25}H_{17}FN_2O_2$ (MH^+) 397.1353; Found 397.1359.

5-(3-methoxyphenyl)-1-(4-methoxyphenyl)-2-(pyridin-4-yl)-1*H*-pyrrole (**55ab**)



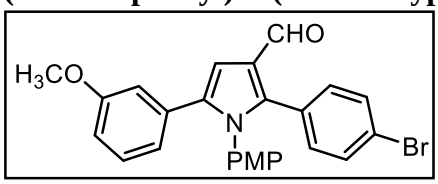
Greenish pasty liquid (70 mg, 61%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.64 (s, 3H), 3.77 (s, 3H), 6.64-6.68 (m, 2H), 6.75-6.79 (m, 3H), 6.91 (d, *J*=8.8Hz, 2H), 6.99 (s, 1H), 7.09-7.15 (m, 3H), 8.54 (d, *J* = 5.1 Hz, 2H), 9.76 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.05, 55.42, 108.17, 113.63, 113.95, 114.34 (2C), 121.24, 124.44, 125.42 (2C), 129.23, 129.37, 129.43 (2C), 132.36, 137.59, 137.71, 139.99, 149.43 (2C), 159.16, 159.30, 186.15; IR (KBr)/cm^{-1} 2924, 1680, 1506, 1456, 1249, 1178; HRMS (ESI): Calcd for $C_{24}H_{20}N_2O_3$ (MH^+) 385.1553; Found 385.1559.

2-(4-chlorophenyl)-5-(3-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (**55ac**)



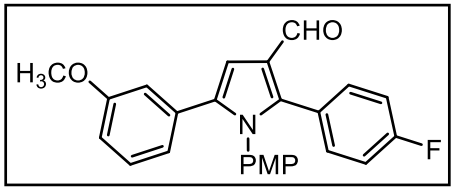
Reddish pasty liquid (75 mg, 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 6H), 6.66 (s, 1H), 6.76-6.79 (m, 4H), 6.83 (d, *J* = 10.1 Hz, 2H), 6.91 (d, *J* = 8.9 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 4H), 9.71 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.25, 55.37, 107.48, 112.99 (2C), 121.20, 124.04, 127.89, 128.36 (2C), 129.15 (2C), 129.54 (2C), 129.62 (2C), 129.77, 130.38, 132.74, 134.73, 136.90, 142.74, 159.05, 159.14, 186.57; (KBr)/cm^{-1} 2956, 1681, 1583, 1487, 1435, 1290, 1153; HRMS (ESI): Calcd for $C_{25}H_{20}ClNO_3$ (MH^+) 418.1211; Found 418.1215.

2-(4-bromophenyl)-5-(3-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (**55ad**)



Colourless oily liquid (79 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H), 6.63 (s, 1H), 6.75 (d, *J* = 8.9 Hz, 3H), 6.81 (d, *J* = 8.2 Hz 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 9.69 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 55.41, 107.51, 112.98, 114.18 (2C), 117.48, 119.52, 120.68, 121.20, 123.05, 123.99, 128.34, 129.16, 129.53 (2C), 131.32 (2C), 132.57 (2C), 136.20, 158.20, 142.72, 159.04, 159.12, 186.61; (KBr)/cm^{-1} 2956, 1666, 1600, 1487, 1315, 1290, 1151; HRMS (ESI): Calcd for $C_{25}H_{20}BrNO_3$ (MH^+) 462.0706; Found 462.0712.

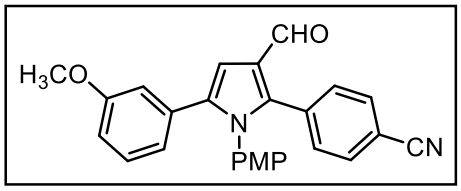
2-(4-fluorophenyl)-5-(3-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole (**55ae**)



Reddish oily liquid (82 mg, 67%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 6H), 6.64 (s, 1H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.80 (d, *J* = 2.4 Hz, 2H), 6.82 (d, *J* = 2.4 Hz, 2H),

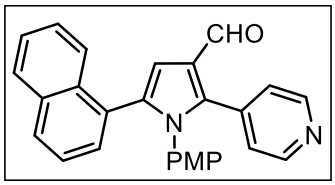
6.89 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 4H), 9.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.09. 55.32, 107.57, 113.03, 114.24 (2C), 117.54, 119.57, 120.73, 121.26, 123.10, 124.04, 129.58 (2C), 129.69, 131.37 (2C), 132.63 (2C), 136.98, 138.26, 142.77, 159.09, 159.17, 186.67; (KBr)/cm^{-1} 2941, 1681, 1454, 1290, 1153; HRMS (ESI): Calcd for $C_{25}H_{20}FNO_3$ (MH^+) 402.1506; Found 402.1508.

4-(3-formyl-5-(3-methoxyphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrol-2-yl)benzonitrile (**55af**)



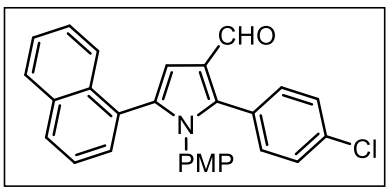
Yellow oily liquid (84 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s,3H), 3.78 (s,3H), 6.63(s, 1H), 6.75 (d, *J* = 8.9 Hz, 3H), 6.89 (d, *J* = 8.8 Hz 3H), 7.12 (d, *J* = 7.8 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.58 (d, *J* = 8.4 Hz 2H), 9.72 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.01, 55.22, 112.93, 113.56, 113.93, 114.17, 114.24, 114.29 (2C), 117.44, 121.19, 121.89, 126.88, 127.84, 129.42 (2C), 131.41, 131.59 (2C), 131.70 (2C), 137.51, 140.85, 157.67, 159.59, 186.14; (KBr)/cm^{-1} 2941, 2225, 1681, 1506, 1435, 1259, 1155; HRMS (ESI): Calcd for $C_{26}H_{20}N_2O_3$ (MH^+) 409.1553; Found 409.1562.

1-(4-methoxyphenyl)-5-(naphthalen-1-yl)-2-(pyridin-4-yl)-1*H*-pyrrole (**55ag**)



Yellow viscous liquid (57 mg, 50%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.61 (s, 3H), 6.751 (d, *J* = 8.5Hz, 2H), 6.76 (d, *J* = 8.1 Hz, 2H), 7.01 (s, 1H), 7.15 (d, *J* = 5.9 Hz, 2H), 7.19 (d, *J* = 7.1 Hz, 1H), 7.31 (t, *J* = 7.3Hz, 8.0 Hz, 1H), 7.43-7.47 (m, 2H), 7.76-7.82 (m, 2H), 7.88-7.90 (m, 1H), 8.55 (d, *J* = 5.6 Hz, 2H), 9.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.18, 110.22, 113.89 (2C), 124.34, 124.69, 125.34 (2C), 125.65, 125.99, 126.48, 128.18, 128.83 (2C), 128.91 (2C), 129.24 129.46, 132.82, 133.34, 135.79, 137.71, 139.27, 149.48 (2C), 158.89, 186.20. (KBr)/cm^{-1} 2956, 1672, 1510, 1433, 1247; HRMS (ESI): Calcd for $C_{27}H_{20}N_2O_2$ (MH^+) 405.1604; Found 405.1612.

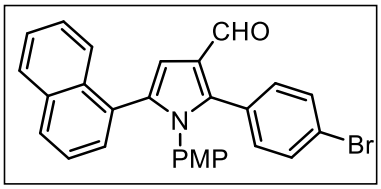
2-(4-chlorophenyl)-1-(4-methoxyphenyl)-5-(naphthalen-1-yl)-1*H*-pyrrole (**55ah**)



Colourless liquid (70 mg, 54%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 6.51 (d, *J* = 8.4 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 2H), 6.99 (s, 1H), 7.28-7.33 (m, 3H), 7.39 (t, *J* = 10.5 Hz, 8.7 Hz, 1H), 7.44-7.47 (m, 2H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.80-7.89 (m, 2H), 7.96 (d, *J* = 9.3 Hz, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.16, 109.59, 113.75 (2C), 123.89, 124.30, 124.72 ,125.85, 125.95, 126.38, 128.15, 128.45

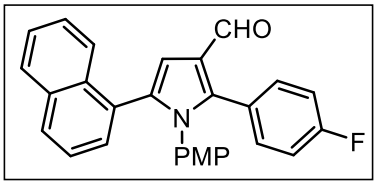
(2C), 128.64, 129.05 (2C),129.20, 129.47, 130.43, 132.31 (2C), 133.39, 134.69, 134.84, 142.00, 150.80, 158.64, 186.69. (KBr)/cm^{-1} 2924, 1678, 1506, 1224, 1184, 1157; HRMS (ESI): Calcd for $C_{28}H_{20}ClNO_2$ (MH^+) 438.1261; Found 438.1268.

2-(4-bromophenyl)-1-(4-methoxyphenyl)-5-(naphthalen-1-yl)-1*H*-pyrrole (**55ai**)



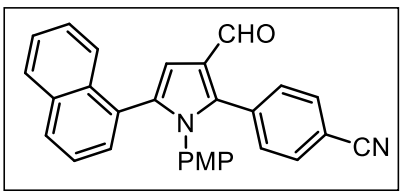
Reddish oily liquid (80 mg, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.63 (s, 3H), 6. 51 (d, *J* = 8.7Hz, 2H), 6.74 (d, *J* = 8.1 Hz, 2H), 6.99 (s, 1H), 7.12 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 7.1 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.34 (d, *J* = 8.1 Hz, 1H), 7.36 (s, 1H), 7.76 (d, *J* = 8.2 Hz, 1H), 7.80-7.82 (m, 1H), 7.89 (d, *J* = 6.7 Hz, 1H), 7.95 (d, *J* = 9.6 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 1H), 9.80 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 55.17, 109.64, 113.75 (2C), 122.98, 123.86, 124.39, 124.72, 125.59,125.83, 126.37, 127.82, 128.14, 128.64, 129.04, 129.24, 129.61, 129.99, 131.37,132.14, 132.90, 133.03, 133.37, 133.93, 134.88, 141.95, 158.65, 186.64; IR (KBr)/cm^{-1} 2953, 1670, 1506, 1456, 1249, 1184; HRMS (ESI): Calcd for $C_{28}H_{20}BrNO_2$ (MH^+) 482.0756 Found 482.0762.

2-(4-fluorophenyl)-1-(4-methoxyphenyl)-5-(naphthalen-1-yl)-1*H*-pyrrole (**55aj**)



Greenish pasty liquid (70 mg, 56%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 6.50 (d, *J* = 8.7 Hz, 2H), 6.75 (d, *J* = 8.2 Hz, 2H), 6.99 (s, 1H), 7.02 (d, *J* = 8.6 Hz, 2H), 7.10 (t, *J* = 8.6 Hz, 1H), 7.18-7.23 (m, 2H), 7.32 (dd, *J* = 14.5, 7.4 Hz, 2H), 7.97 (d, *J* = 6.7 Hz, 2H), 8.02 (t, *J* = 6.0 Hz, 1H), 8.10 (d, *J* = 8.8 Hz, 1H), 9.79 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.53, 109.54, 112.70, 114.69 (2C), 122.39, 126.85, 126.96, 128.01, 128.12, 128.19, 128.30 (2C), 128.55, 128.70, 128.80 (2C), 129.36, 129.64 (2C), 129.94, 130.56, 133.16, 139.99, 147.35, 159.59, 160.17, 186.38; IR (KBr)/cm^{-1} 2964, 1684, 1506, 1296, 1184, 1157; HRMS (ESI): Calcd for $C_{28}H_{20}FNO_2$ (MH^+) 422.1556; Found 422.1562.

4-(3-formyl-1-(4-methoxyphenyl)-5-(naphthalen-1-yl)-1*H*-pyrrol-2-yl) benzonitrile (**55ak**)



Yellow liquid (75 mg, 59%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.62 (s, 3H), 6.51 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.1 Hz, 2H), 7.03 (s, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.30 (dd, *J* = 15.3 Hz,14.5Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.42-7.47 (m, 4H), 7.59 (d, *J* = 8.4 Hz, 2H), 9.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.21, 110.34, 112.00, 113.88 (2C), 118.27, 122.17, 124.23, 124.71, 125.65, 126.00, 126.42, 127.96, 128.20, 128.36,

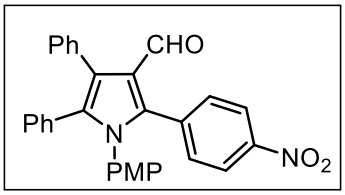
128.87, 128.93, 129.27, 131.57, 131.75, 132.83, 133.07, 133.36, 133.87, 134.40, 135.60, 140.08, 158.85, 186.16; IR (KBr)/cm^{-1} 2954, 2225, 1690, 1514, 1315, 1247, 1180; HRMS (ESI): Calcd for $C_{29}H_{20}N_2O_2$ (MH^+) 429.1603 Found 429.1606.

4.9 General procedure for the synthesis of fully substituted 2,4,5-tri-aryl pyrrole-3-carboxaldehydes (56)

N- Bromosuccinimide (NBS) (0.3 mmol) was added to the stirred solution of pyrrole (**54 and 55**) (0.3 mmol) in CH_3CN (4.0 mL) at room temperature and further heated at 80 ^oC for 4 hrs. The reaction was cooled to room temperature and solvent were evaporated under reduced pressure. The crude material was taken in saturated $NaHCO_3$ solution and extracted with ethyl acetate (2 x 5 mL), the combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated under vacuum. Corresponding intermediate bromo compound were obtained in good yields in all cases (65-74%) after simple chromatographic purification using EtOAc/hexane. To the stirred solution of crude bromo compound in DMF (3.0 mL) were added $PhB(OH)_2$ (1.0 equiv.), Pd $(PPh_3)_4$ (10 mol %) and K_2CO_3 (2M solution, 78 μL, 0.15 mmol) under an inert atmosphere. The reaction was then heated to 110 ^oC for 4 hrs. After complete consumption of the intermediate bromo compound on TLC, the reaction was cooled and filtered through celite. After standard work up and chromatographic purification using (Hexane: EtOAc = 20:1) gave compound (**56**) in good yields (64-74%).

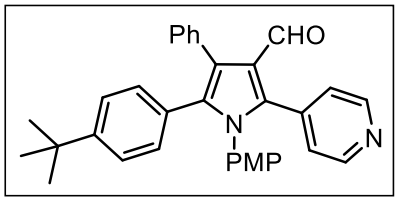
4.10 Analytic data of synthesized coupling products (56a-56l)

1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4, 5-diphenyl-1*H*-pyrrole-3-carbaldehyde (56a)



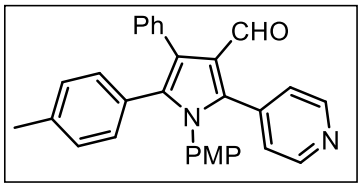
Yellow pasty liquid (104 mg, 74%); ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 6.67 (d, *J* = 8.9 Hz, 2H), 6.85 (d, *J* = 8.9 Hz, 2H), 6.93 (d, *J* = 6.7 Hz, 2H), 7.07-7.13 (m, 3H), 7.17-7.20 (m, 1H), 7.27 (bs, 4H), 7.43 (d, *J* = 8.8 Hz, 2H), 8.12 (d, *J* = 8.8 Hz, 2H), 9.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.31, 114.06 (2C), 120.93, 122.93 , 125.66, 126.95, 127.52, 127.86 (2C), 127.97 (2C), 128.12, 129.28, 129.41, 129.69 (2C), 130.30, 130.93 (2C), 131.17 (2C), 132.09 (2C), 132.81, 134.69, 137.17, 147.21, 159.08, 187.02; IR (KBr)/cm^{-1} 2923, 2854, 1681, 1596, 1342, 1242, 1034; HRMS (ESI): Calcd for $C_{30}H_{22}N_2O_4$ (MH^+) 475.1659; Found 475.1664.

5-(4-*tert*-butylphenyl)-1-(4-methoxyphenyl)-4-phenyl-2-(pyridin-4-yl)-1*H*-pyrrole (**56b**)



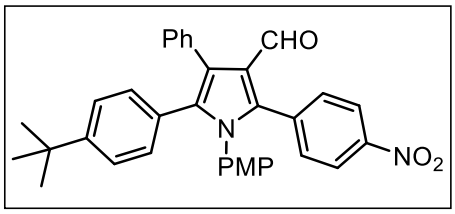
Yellow pasty liquid (100 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 9H), 3.70 (s, 3H), 6.66 (d, 7.4 Hz, 2H), 6.78 (d, *J* = 7.4 Hz, 2H), 7.09 (d, *J* = 7.0 Hz, 2H), 7.22 (d, *J* = 4.9 Hz, 2H), 7.29 (d, *J* = 7.1 Hz, 2H), 7.39 (s, 5H), 8.67 (d, *J* = 4.8 Hz, 2H), 9.93 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.10 (3C), 34.59, 55.37, 99.74, 114.28 (2C), 120.36, 124.97, 125.01, 125.64, 126.19, 126.25, 127.44 (2C), 128.60, 129.29 (2C), 129.47, 130.28, 130.32, 133.56 (3C), 135.85, 136.00, 139.45, 146.45, 146.48, 151.47, 159.37, 185.81; HRMS (ESI): Calcd for $C_{33}H_{30}N_2O_2$ (MH^+) 487.2385; Found 487.2392.

1-(4-methoxyphenyl)-4-phenyl-2-(pyridin-4-yl)-5-(p-tolyl)-1*H*-pyrrole-3-carbaldehyde (**56c**)



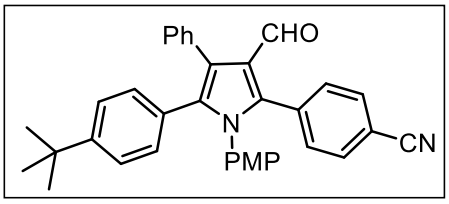
Yellow viscous liquid (95 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.73 (s, 3H), 6.66 (d, *J* = 8.9 Hz, 2H), 6.79 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 3.0 Hz, 3H), 7.10 (d, *J* = 6.0 Hz, 2H), 7.38 – 7.41 (m, 1H), 7.44 – 7.49 (m, 2H), 7.53 – 7.57 (m, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 8.54 (d, *J* = 6.1 Hz, 2H), 9.90 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 21.30, 55.34, 114.20 (2C), 120.17, 125.60, 126.05, 128.43 (2C), 128.55 (2C), 128.86 (2C), 128.95, 129.41 (2C), 130.68 (2C), 131.92, 131.95, 132.04 (2C), 132.14 (2C), 133.63, 133.49, 149.06 (2C), 159.30, 185.72; HRMS (ESI): Calcd for $C_{30}H_{24}N_2O_2$ (MH^+) 445.1916; Found. 445.1922.

5-(4-(*tert*-butyl)phenyl)-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4-phenyl-1*H*-pyrrole (**56d**)



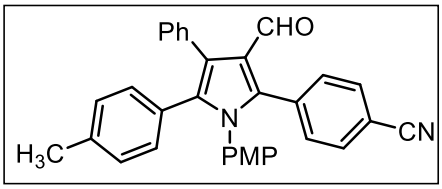
Reddish brown liquid (112 mg, 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 3.74 (s, 3H), 6.68 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 3.1 Hz, 2H), 6.87 (d, *J* = 3.5 Hz, 2H), 7.10 (d, *J* = 8.4 Hz, 2H), 7.29 (s, 5H), 7.43 (d, *J* = 8.9 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H), 9.86 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.14 (3C) , 34.46, 55.35, 113.98 (2C), 120.97, 122.89 (2C), 123.01, 124.72 (2C), 125.03, 125.48, 126.84, 127.92 (2C), 129.45, 129.72 (2C), 130.37, 130.69 (2C), 130.99 (2C), 132.10 (2C), 136.97, 137.30, 147.15, 150.42, 159.01, 187.05; HRMS (ESI): Calcd for $C_{34}H_{30}N_2O_2$ (MH^+) 531.2284; Found 531.2290.

4-(5-(4-*tert*-butylphenyl)-3-formyl-1-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrol-2-yl) benzonitrile (**56e**)



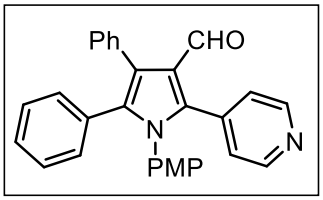
Yellow pasty liquid (104 mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 3.69 (s, 3H), 6.61 (d, *J* = 8.1 Hz, 2H), 6.72 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 6.7 Hz, 2H), 7.04 (t, *J* = 7.7 Hz, 3H), 7.23 (d, *J* = 8.3 Hz, 5H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 2H), 9.83 (s, 1H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.15 (3C) , 34.61, 55.34, 112.26, 114.11 (2C), 118.53, 120.82, 124.97 (2C), 125.18, 127.14, 127.83 (2C), 129.03, 129.71 (2C), 130.38 (2C), 130.71 (2C), 130.96 (2C), 131.51 (2C), 131.87 (2C), 134.01, 134.59, 138.58, 151.35, 159.20, 186.92; HRMS (ESI): Calcd for $C_{35}H_{30}N_2O_2$ (MH^+) 511.2385; Found 511.2392.

4-(3-formyl-1-(4-methoxyphenyl)-4-phenyl-5-p-tolyl-1*H*-pyrrol-2-yl)benzonitrile (**56f**)



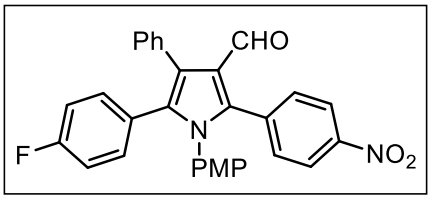
Brownish pasty liquid (95mg, 68%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.17 (s, 3H), 3.69 (s, 3H), 6.62 (d, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 12.4 Hz, 2H), 6.78(t, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 3.4 Hz, 1H), 7.21 (s, 5H), 7.31 (d, *J* = 7.6 Hz, 2H), 7.50 (d, *J* = 7.9 Hz, 2H), 9.78 (s, 1H) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.13, 55.26, 111.69, 113.94 (2C), 115.55, 118.51, 120.53, 126.79, 128.27, 128.50, 128.57 (2C), 128.73, 128.84, 128.99, 129.19, 129.38, 129.55, 129.67 (2C), 129.78, 130.69, 130.94 (2C), 131.40, 131.53, 131.75, 131.83, 137.19, 158.94, 187.05; HRMS (ESI): Calcd for $C_{32}H_{24}N_2O_2$ (MH^+) 469.1916; Found 469.1922.

1-(4-methoxyphenyl)-4, 5-diphenyl-2-(pyridin-4-yl)-1*H*-pyrrole-3-carbaldehyde (**56g**)



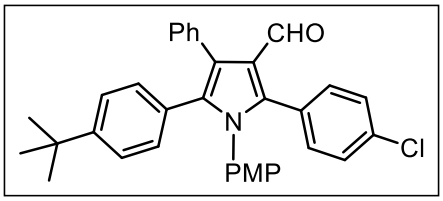
Reddish oily liquid (80 mg, 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (s, 3H), 6.66 (d, *J* = 8.7 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.11 (dd, *J* = 4.3, 1.5 Hz, 3H), 7.18 (dd, *J* = 4.5, 2.1 Hz, 2H), 7.21-7.24 (m, 2H), 7.29 (t, *J* = 4.5, Hz, 3H), 7.54 (d, *J* = 6.5 Hz, 2H), 8.55 (d, *J* = 5.8 Hz, 2H), 9.91 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.42, 114.72 (2C), 126.71, 127.22, 128.26, 128.36, 128.61 (2C), 128.73 (2C), 128.81, 128.94, 129.25, 130.78, 130.89, 131.59 (2C), 132.05 (2C), 132.15 (2C), 132.22, 132.24, 132.36, 133.81, 142.83, 159.77, 186.00; HRMS (ESI): Calcd for $C_{29}H_{22}N_2O_2$ (MH^+); 431.1759 Found 431.1765.

(4-fluorophenyl)-1-(4-methoxyphenyl)-2-(4-nitrophenyl)-4-phenyl-1*H*-pyrrole (**56h**)



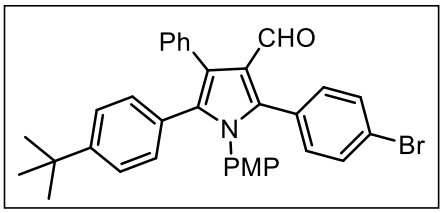
Yellow pasty liquid (105 mg, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 6.79 (d, *J* = 8.9 Hz, 2H), 6.77-6.85 (m, 4H), 6.90 (dd, *J* = 8.8 Hz, 8.8Hz 2H), 7.04 (t, *J* = 8.6 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 2H), 7.37 (dd, *J* = 8.9 Hz, 8.9 Hz, 1H),7.42 (d, *J* = 8.9 Hz, 2H), 8.13 (d, *J* = 8.8 Hz, 2H) 9.85 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.33, 114.15 (2C), 115.01, 115.18, 115.52, 115.69, 122.97 (2C), 125.74, 127.08, 127.19, 127.26, 128.07 (2C), 129.01, 129.65 (2C), 130.85 (2C), 132.06 (2C), 132.60, 132.82, 132.89, 136.98, 137.29, 147.22, 159.15, 186.91; IR (KBr)/cm^{-1} 2923, 1728, 1512, 1350, 1226; HRMS (ESI): Calcd for $C_{30}H_{21}FN_2O_4$ (MH^+) 493.1564; Found 493.1571.

5-(4-*tert*-butylphenyl)-2-(4-chlorophenyl)-1-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole (**56i**)



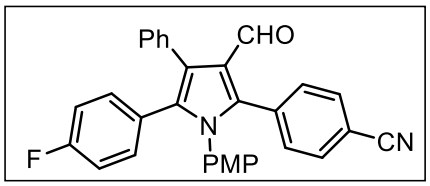
Reddish oily liquid (103 mg, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H), 3.76 (s, 3H), 6.68 (d, *J* = 8.9 Hz, 2H), 6.85 (t, *J* = 8.8 Hz, 4H), 7.08 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.5 Hz, 2H), 7.28 (s, 7H), 9.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.15 (3C), 34.42, 55.31, 113.76 (2C), 120.58, 124.60 (2C), 126.53, 127.42, 127.68 (2C), 128.11 (2C), 128.34, 129.51, 129.78 (2C), 130.42, 130.75 (2C), 130.96 (2C), 132.56 (2C), 133.55, 134.08, 134.39, 140.43, 150.10, 158.71, 187.05; HRMS (ESI): Calcd for $C_{34}H_{30}ClNO_2$ (MH^+) 520.2043; Found 520.2049.

2-(4-bromophenyl)-5-(4-*tert*-butylphenyl)-1-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole (**56j**)



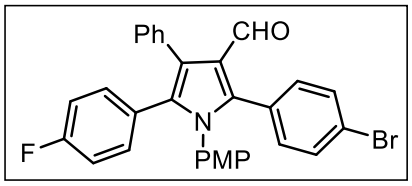
Brownish oily liquid (108 mg, 65%);^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 3.73 (s, 3H), 6.66 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.27-7.30 (m, 3H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.43 (d, *J* = 7.8 Hz, 2H), 9.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.17 (3C), 34.43, 55.29, 113.70 (2C), 120.65, 124.57 (2C), 126.40 (2C), 127.60 (2C), 128.80 (2C), 129.86 (2C), 130.17, 130.51, 130.84 (2C), 130.98 (2C), 131.79 (2C), 133.57, 133.85, 134.14, 140.21,150.03, 158.64, 187.34; HRMS (ESI): Calcd for $C_{34}H_{30}BrNO_2$ (MH^+) 564.1538; Found 564.1543.

4-(5-(4-fluorophenyl)-3-formyl-1-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrol-2-yl)benzonitrile (56k)



Brownish pasty liquid (92 mg, 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 6.77 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 6.88-6.93 (m, 2H), 6.98 (t, *J* = 8.7 Hz, 2H), 7.15-7.18 (m, 1H), 7.27-7.32 (m, 6H), 7.37 (d, *J* = 8.5 Hz, 2H), 9.83 (s, 1H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 55.34, 111.91, 114.14 (2C), 114.96, 118.48, 125.51, 127.04, 128.03 (2C), 128.69, 129.11, 129.41 (2C), 129.69 (2C), 130.88 (2C), 131.51 (2C), 131.86 (2C), 132.66 (2C), 132.79, 132.96, 133.74, 134.99, 159.17, 159.39,186.93; HRMS (ESI): Calcd for $C_{31}H_{21}FN_2O_2$ (MH^+) 473.1665; Found 473.1671.

2-(4-bromophenyl)-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-4-phenyl-1*H*-pyrrole (56l)

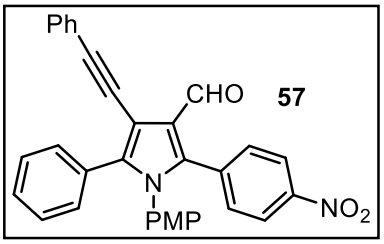


Yellow liquid (100 mg, 64 %); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 6.68 (d, *J* = 8.9 Hz, 2H), 6.74– 6.83 (m, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.29 (dd, *J* = 16.6, 6.0 Hz, 4H), 7.34–7.38 (m, 1H), 7.43 (t, *J* = 7.5 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 9.87 (s, 1H); ^{13}C NMR (25 MHz, $CDCl_3$) δ 55.30, 113.90 (2C), 133.04, 114.80, 115.01, 124.03, 126.48 (2C), 126.67, 127.30, 127.74 (2C), 128.60, 128.82 (2C), 129.57, 129.84 (2C), 130.88 (2C), 131.75 (2C), 132.96, 133.04, 133.52, 140.16, 140.94, 158.85, 187.13; HRMS (ESI): Calcd for $C_{31}H_{21}FN_2O_2$ (MH^+) 524.0662; Found 524.0668.

4.11 Experimental procedure for the synthesis of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-5-phenyl-4-(phenylethynyl)-1*H*-pyrrole-3-carbaldehyde (57)

N- Bromosuccinimide (NBS) (0.3 mmol) was added to the stirred solution of pyrrole (**56c**) (0.3 mmol) in CH_3CN (4.0 mL) at rt and further heated at 80 ^{o}C for 4 hrs. The reaction was cooled to room temperature and solvent was evaporated under reduced pressure. The crude material was taken in saturated $NaHCO_3$ solution and extracted with ethyl acetate (2 x 5 mL), the combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated under vacuum. Corresponding intermediate bromo compound were obtained in good yields (74%) after simple chromatographic purification using EtOAc/hexane. To the stirred solution of crude bromo compound (0.10 mmol, 1.0 equiv.) in DMF (3.0 mL) triethylamine was added then purged with N_2 under reduced pressure, repeated by two times were added phenyl acetylene (0.15mmol, 1.5 equiv.), CuI catalyst (10 mol %.), Pd $(PPh_3)_4$ (10 mol %) and further purged with N_2 for 15 sec.

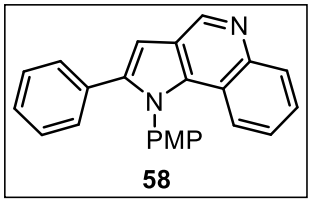
under vaccum. The reaction was then heated to 110 °C for 5 hrs. After complete consumption of the intermediate bromo-compound on TLC, reaction was cooled and filtered through celite. After standard work up and chromatographic purification using (Hexane: EtOAc = 20:1) gave compound (**57**) as brownish red oily liquid (106 mg, 72%);



^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (s, 3H), 6.71 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 7.28-7.32 (m, 8H), 7.38 (d, *J* = 8.7 Hz, 2H), 7.46 – 7.43 (m, 2H), 8.12 (d, *J* = 8.7 Hz, 2H), 10.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.38, 81.95, 93.60, 114.38 (2C), 122.97 (2C), 127.99 (2C), 128.06, 128.13, 128.26 (2C), 128.57, 128.61, 128.83, 128.89, 129.48 (2C), 130.08 (2C), 131.39 (2C), 131.85, 132.07 (2C), 136.15, 136.94, 139.81, 147.43, 159.40, 185.90; HRMS (ESI): Calcd for $C_{32}H_{22}N_2O_4$ (MH^+) 499.1658; Found 499.1662.

4.12 Experimental procedure for the synthesis of compound (**58**)

To a mixture of compound (**54a**) (50 mg, 0.15 mmol), Fe powder (86.9 mg, 1.55 mmol, 10.0 equiv.) and NH_4Cl (100 mg, 1.8 mmol, 12.0 equiv.) in EtOH:H_2O (5 mL, 4:1) was heated at 80 °C for 10 h. Afterwards the reaction mixture was concentrated under reduced pressure. The crude residue was extracted with ethyl acetate. The combined organic solvent evaporated under reduced pressure followed by purification through a pad of silica-gel (eluent:hexane/ethyl acetate = 3:1) afforded the pure product (**58**) as pasty yellow liquid (28 mg, 67% yield).

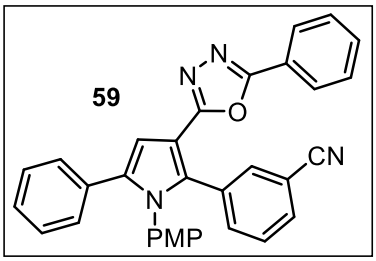


^{1}H NMR (400 MHz, $CDCl_3$) δ 9.24 (s, 1H), 8.23 (d, *J* = 8.3 Hz, 1H), 7.53 (ddd, *J* = 8.3, 6.7, 1.6 Hz, 1H), 7.32 (d, *J* = 8.9 Hz, 2H), 7.27 (s, 5H), 7.21 (ddd, *J* = 9.8, 7.6, 1.2 Hz, 2H), 7.02 (d, *J* = 8.9 Hz, 2H), 6.98 (s, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.01, 157.90, 152.63, 150.45, 145.38, 139.28, 135.82, 131.75, 130.38(2C), 129.48 (2C), 128.19 (2C), 127.81, 126.49, 125.62, 125.60, 120.68, 118.33, 114.88 (2C), 103.66, 55.56; HRMS (ESI): Calcd for $C_{24}H_{18}N_2O$ (MH^+) 351.1498; Found 351.1502.

4.13 General experimental procedure for compound (**59**)

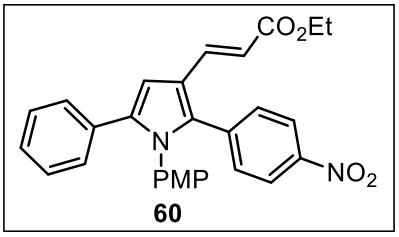
A mixture of (**54ab**) (0.08g, 0.24 mmol, 1.0 equiv) and 4-nitrobenzohydrazide (0.044g, 0.24 mmol, 1.0 equiv) in methanol (3 mL) was stirred for 2 hours under 80 °C and then concentrated under vacumm. Then followed by the addition of IBD (0.08g, 0.24 mmol, 1.0 equiv) dissolved in acetonitrile (3mL) in the reaction vessel and stirred at room temperature for one hour. The

mixture was then concentrated in vacuo. To the residue was added H_2O (10 mL) and the resulting mixture was extracted with ethylacetate (10 mL x 3). The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel using (eluent: hexane/ethyl acetate = 2:1) affording final product (**59**) as yellow foamy solid (92 mg, 76% yield).



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 7.9, 1.7 Hz, 2H), 7.65 – 7.62 (m, 1H), 7.58 – 7.62 (m, 1H), 7.53 – 7.57 (m, 1H), 7.47 (td, *J* = 5.8, 3.7 Hz, 3H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.24 (dd, *J* = 5.2, 1.9 Hz, 2H), 7.13– 7.17 (m, 2H), 7.12 (s, 1H), 6.91 (d, *J* = 8.9 Hz, 2H), 6.74 (d, *J* = 8.9 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.24, 161.64, 159.00, 137.01, 135.85, 134.77, 133.45, 132.58, 131.54, 131.41, 131.33, 130.01, 129.79, 129.62 (2C), 128.94 (2C), 128.61 (2C), 128.18 (2C), 127.31, 126.45 (2C), 123.81, 118.31, 114.18 (2C), 111.91, 108.97, 107.85, 55.31; HRMS (ESI): Calcd for $C_{32}H_{22}N_4O_2$ (MH^+) 495.1821; Found 495.1826.

4.14 Synthetic procedure for compound (**60**)



To the compound (**54c**) (0.16 mmol) in dry THF (3 ml), added diethyl phosphano acetate (0.19 mmol, 1.2 eq) at 0 ^{o}C and followed by NaH (2.5 eq, 0.41 mmol) under nitrogen atmosphere, and stirred for 3 hours which was monitored by TLC. The reaction was quenched with $NaHCO_3$ solution (10 ml) and extracted with ethyl acetate three times (10x3), and washed with brine (10 ml). The organic layer was dried over sodium sulphate and solvent was evaporated under reduced pressure followed by column chromatography (hexane: ethyl acetate) obtained (**60**) as yellow solid (82%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.9 Hz, 2H), 7.60 – 7.51 (m, 1H), 7.24 (d, *J* = 8.9 Hz, 3H), 7.22 (d, *J* = 2.7 Hz, 2H), 7.10 (ddd, *J* = 6.0, 4.5, 2.8 Hz, 2H), 6.86 (d, *J* = 9.0 Hz, 2H), 6.76 (s, 1H), 6.72 (d, *J* = 9.0 Hz, 2H), 6.31 (d, *J* = 15.6 Hz, 1H), 4.22 (q, *J* = 7.1 Hz, 2H), 3.76 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.63, 158.92, 146.73, 137.80, 137.44, 137.11, 135.20, 131.65, 131.41 (2C), 130.20, 129.47(2C), 128.72 (2C), 128.13 (2C), 127.28, 123.25 (2C), 120.28, 115.78, 114.20 (2C), 107.24, 60.18, 55.31, 14.33; HRMS (ESI): Calcd for $C_{28}H_{24}N_2O_5$ (MH^+) 469.1763; Found 469.1769.

A representative ^{1}H and ^{13}C NMR of (**54c and 56c)** are shown in (**Figure 4.2 and 4.3)**.

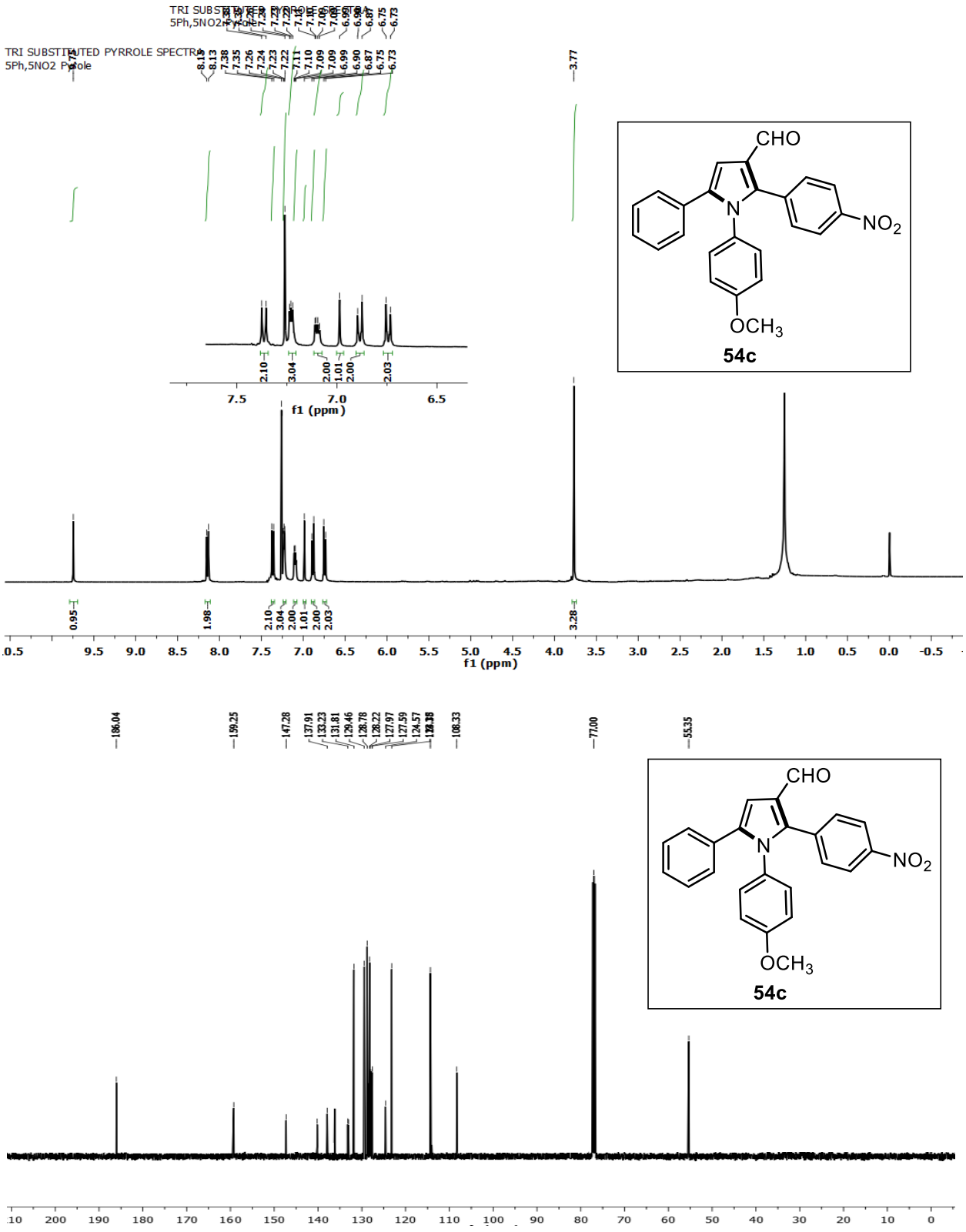


Figure 4.2 ^{1}H and ^{13}C NMR spectra of 1-(4-methoxyphenyl)-2-(4-nitrophenyl)-5-phenyl-1H-pyrrole-3-carbaldehyde (**54c**)

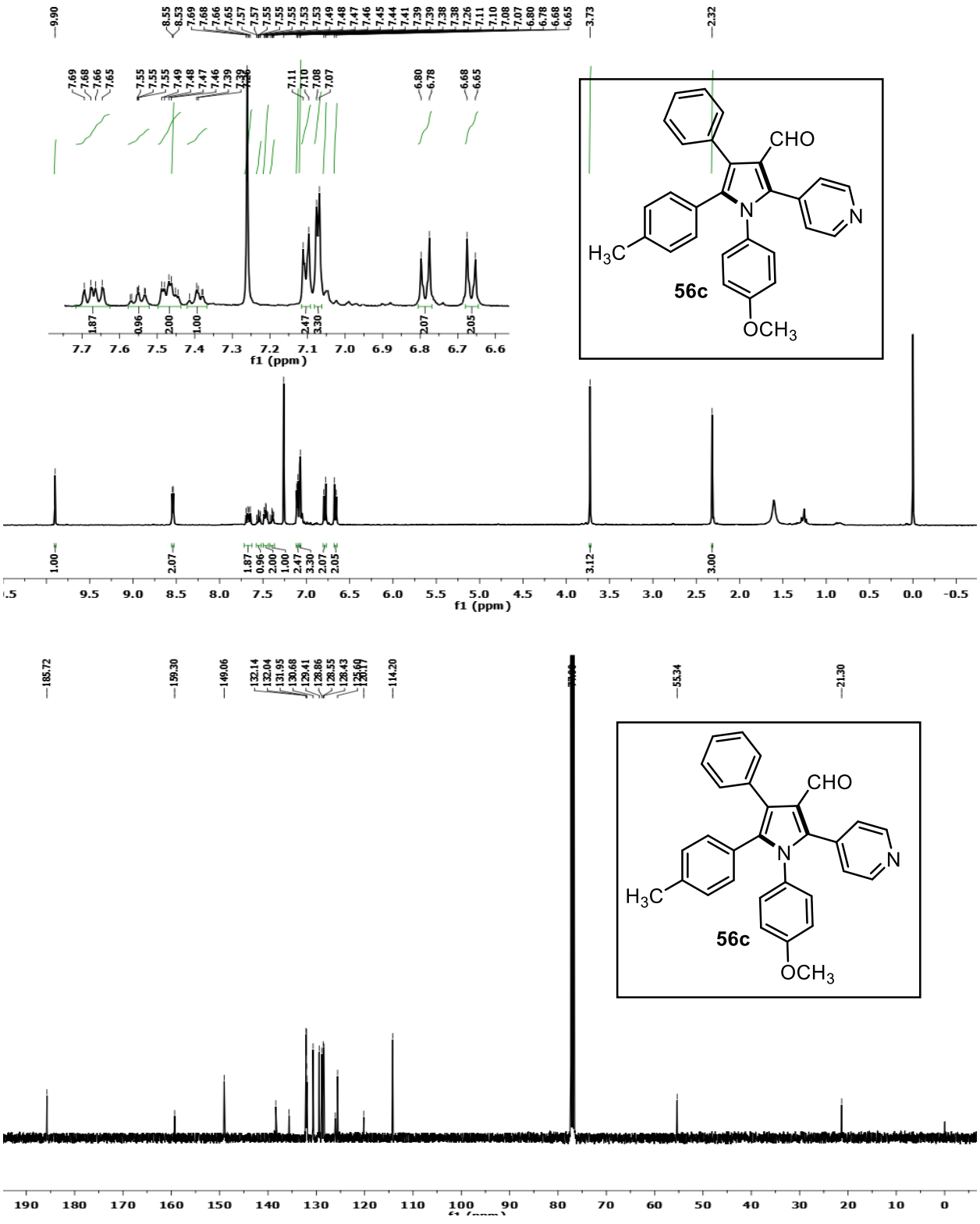


Figure 4.3 ^{1}H and ^{13}C NMR spectra of 1-(4-methoxyphenyl)-4-phenyl-2-(pyridin-4-yl)-5-(p-tolyl)-1H-pyrrole-3-carbaldehyde (**56c**)

4.15 Crystal structure of 1-(4-methoxyphenyl)-2-(3-nitrophenyl)-5-phenyl-1*H*-pyrrole-3 carbaldehyde (54b) with [CCDC No. 1400573]

Table 4.5 Crystal data for (**54b**)

Crystal description	white block
Crystal size	0.3 X 0.2 X 0.2 mm
Empirical formula	$C_{24}H_{18}N_2O_4$
Formula weight	398.40
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a= 23.3836(15), b= 7.8481(5), c= 24.1515(17) Å, β = 115.063(8)
Crystal system	monoclinic
Space group	P 2_1/n
Unit cell volume	4014.9(5)
No. of molecules per unit cell, Z	8
Temperature	293(2) K
Absorption coefficient	0.091 mm^{-1}
F(000)	1664
Scan mode	ω scan
θ range for entire data collection	3.58 <θ< 25.99
Range of indices	h= -26 to 28, k= -9 to 9, l= -28 to 29
Reflections collected / unique	15763/ 7851
Reflections observed (I > 2σ (I))	3359
R_{int}	0.0524
R_{sigma}	0.1111
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	544
Final R	0.0551
wR (F^2)	0.0765
Weight	$1/[\sigma^2(F_o^2)+(0.0133P)^2+0.0000P]$ Where $P=[F_o^2+2F_c^2]/3$
Goodness-of-fit	0.894
Final residual electron density	$-0.172<\Delta\rho<0.152$ eÅ^{-3}

The compound 1-(4-methoxyphenyl)-2-(3-nitrophenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde, $C_{24}H_{18}N_2O_4$, crystallizes in the monoclinic space group P 21/n with the unit-cell parameters: a= 23.3836(15), b= 7.8481(5), c= 24.1515(17) Å, β = 115.063(8) 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 0.0551 for 3359 observed reflections. X-ray intensity data of 15763 reflections (of which 7851 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 a least-squares fit of angular settings of 3935 reflections in the θ range 3.80 to 28.50º**.** The intensities were measured by ω scan mode for θ ranges 3.58 to 25.99º. 3359 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 = 0.0551 and wR (F^2) = 0.0765 for the observed data. Residual electron densities ranged from -0.172 < Δρ < 0.152 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 4.5**). An ORTEP view of the compound with atomic labeling is shown in (**Figure 4.4**). The geometry of the molecule was calculated using the WinGX, PARST, and PLATON software.

An *ORTEP* view of the molecule 1-(4-methoxyphenyl)-2-(3-nitrophenyl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde, (**54b**) showing the atom-labelling scheme and H atoms are shown as small spheres of arbitrary radii as shown in (**Figure 4.4**).

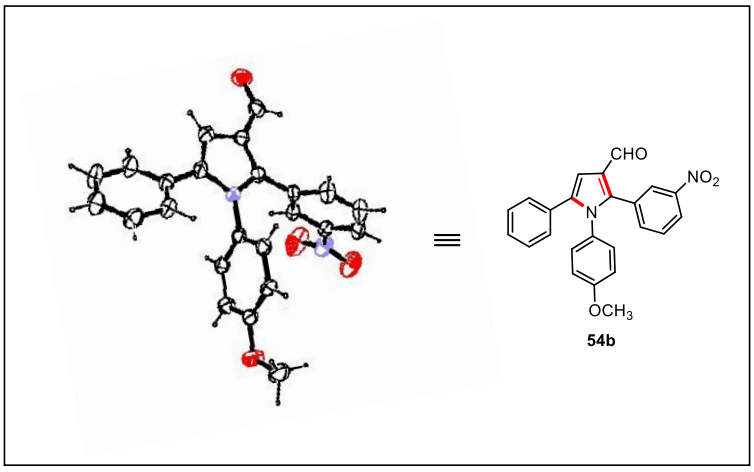


Figure 4.4 Single-crystal X-ray analysis of **54b**

4.16 Crystal structure of 1-(4-methoxyphenyl)-2-(naphthalen-2-yl)-5-phenyl-1*H*-pyrrole-3-carbaldehyde (54r) with [CCDC No. 1007133]

Table 4.6 Crystal data for **52r**

CCDC No	**1007133**
Crystal description	White block shaped
Crystal size	0.30 x 0.20 x 0.20 mm
Empirical formula	$C_{28}H_{21}N_1O_2$
Formula weight	403.46
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a = 12.6491(8), b = 7.9932(4), c = 21.9541(13) Å, β= 105.450(7)
Crystal system	monoclinic
Space group	$P2_1/c$
Unit cell volume	2139.5(2) $Å^3$
Density (calculated)	1.253 Mgm^{-3}
No. of molecules per unit cell, Z	4
Temperature	273(2) K
Absorption coefficient(μ)	0.078 mm^{-1}
F (000)	848
Scan mode	omega scan
θ range for entire data collection	$3.77< \theta < 26.00^{o}$
Reflections collected / unique	7999/4184
Reflections observed ($I > 2\sigma(I)$)	2249
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	280
Final R	0.0489
$wR(F^2)$	0.1114
Weight	$1/[\sigma^2(\Phi_o^2)+(0.0277\Pi)^2+0.00P]$ where $P=[F_o^2+2F_c^2]/3$
Goodness-of-fit	0.918
$(\Delta/\sigma)_{max}$ in the final cycle	0.008
Final residual electron density	$-0.172< \Delta\rho <0.158$ $eÅ^{-3}$
Measurement	*X'calibur system – Oxford diffraction make, U.K.*

The title compound, 1-(4-methoxyphenyl)-2-(naphthalen-2-yl)-5-phenyl-1*H*-pyrrole-3-carboxaldehyde, (**54r)** crystallizes in the monoclinic space group $P2_1/c$ with the following unit-cell parameters: a = 12.6491(8), b = 7.9932(4), c = 21.9541(13) Å, β= 105.450(7), Z = 4. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data and refined by full-matrix least-squares procedures to a final R-value of 0.0489 for 2249 observed reflections.

X-ray intensity data of 7999 reflections (of which 4184 unique) were collected at room temperature on a CCD area-detector diffractometer (*X'calibur system – Oxford diffraction make, U.K.*) 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 intensities were measured by ω scan mode for θ ranges 3.77 to 26.0°. 2249 reflections were treated as observed ($I > 2\sigma(I)$). Data were corrected for Lorentz and polarisation factors. All the hydrogen atoms were geometrically fixed and allowed to ride on the corresponding non-hydrogen atoms with C-H= 0.93-0.96 Å, and $U_{iso} = 1.5U_{eq}$ of the attached C atom for methyl H atoms and 1.2 U_{eq} for other H atoms. The final refinement cycles converged to an R = 0.0489 and wR (F^2) = 0.1114 for the observed data. Residual electron densities ranged from -0.172 to 0.158 eÅ^{-3}. The crystallographic data are summarized in (**Table 4.6**).

An *ORTEP* view of the molecule 1-(4-methoxyphenyl)-2-(naphthalen-2-yl)-5-phenyl-1*H*-pyrrole-3-carboxaldehyde, (**54r**) showing the atom-labelling scheme and H atoms are shown as small spheres of arbitrary radii as shown in (**Figure 4.5**).

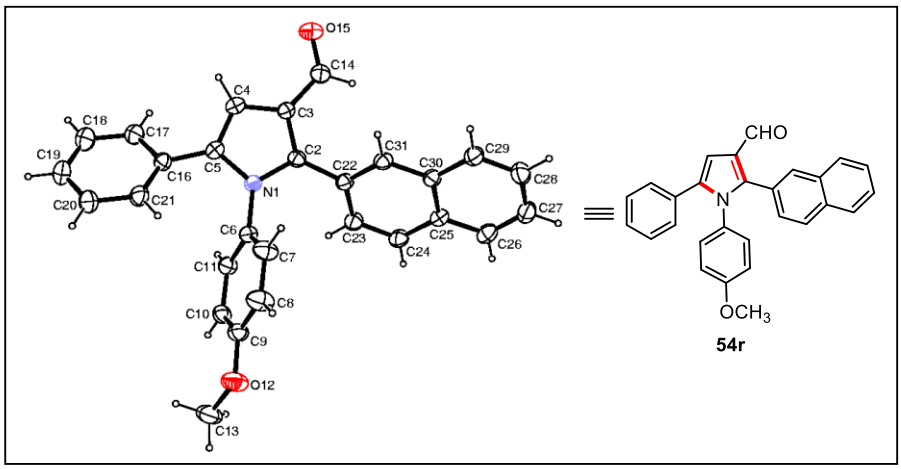


Figure 4.5 Single-crystal X-ray analysis of **54r**

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Chapter V

Rapid synthesis of *N*-aryl substituted pyrrolo-[2, 3-*d*]pyridazin-7-ones

5.1 Introduction

Novel and under explored heterocyclic scaffolds exhibiting valuable biological activity are vital for the drug discovery and development process. Efficient synthetic approaches towards such scaffolds are instrumental to the rapid synthesis and evaluation of these compounds. Multicomponent reactions (MCRs)[1-9] and cascade reactions[10-12] are important tools to meet these goals, because several bond forming steps are combined in a single reaction vessel to form a new product containing portions of all components, are well suited for this purpose. As a result, fewer synthetic steps are required for the construction of a given target molecule. MCRs are one-pot process and are attractive in terms of atom- and step-economy, operational simplicity, and environmental friendliness. This efficient and precise assembly of molecular diversity is one of the key aspects in library synthesis and medicinal chemistry.

Heterocycles are among the most frequently encountered scaffolds in drugs and pharmaceutically relevant substances. In particular, pyridazinones are important class of heterocycles which have been intensively studied on account of their various exciting biological properties. These are versatile pharmacophore of medicinal significance and have drawn a considerable attention in the field of research and development during the last decade due to their diverse pharmacological activities and therapeutic applications.[13-16] Pyrrolo-pyridazinones and their associated derivatives are compounds extensively explored in the literature, due to the various biological properties that members of this system have. Pyridazinones and their *N*-aryl substituted derivatives are building blocks found in many biologically active compounds such as pharmaceuticals and pesticides (e.g., herbicides: Chloridazon, Norflurazon, Oxapyrazon, Flufenpyr, Dimidazon; fungicide: Diclomezine; insecticides: Pyridaphenthion, Pyridaben).[17-18] Differently substituted pyridazinones have been found to have potential antibacterial, antifungal and antiviral including anti-HIV activities, anticancer, analgesic & anti-inflammatory, anticonvulsant, cardiotonic & hypotensive and antiulcer activities.[19-28] Phthalazine derivatives are a class of attractive heterocycles found to be potentially useful to treat many diseases, for instance, Zopolrestat as a potent aldose reductase inhibitor for chronic diabetes,[29] and Aurora-Akinase inhibitors as antitumor agents[30]. The heterocyclic pyridazinones represents an important class of privileged structures in medicinal chemistry that presents an increasing interest in modern drug design and discovery (**Figure 5.1**).[31-40]

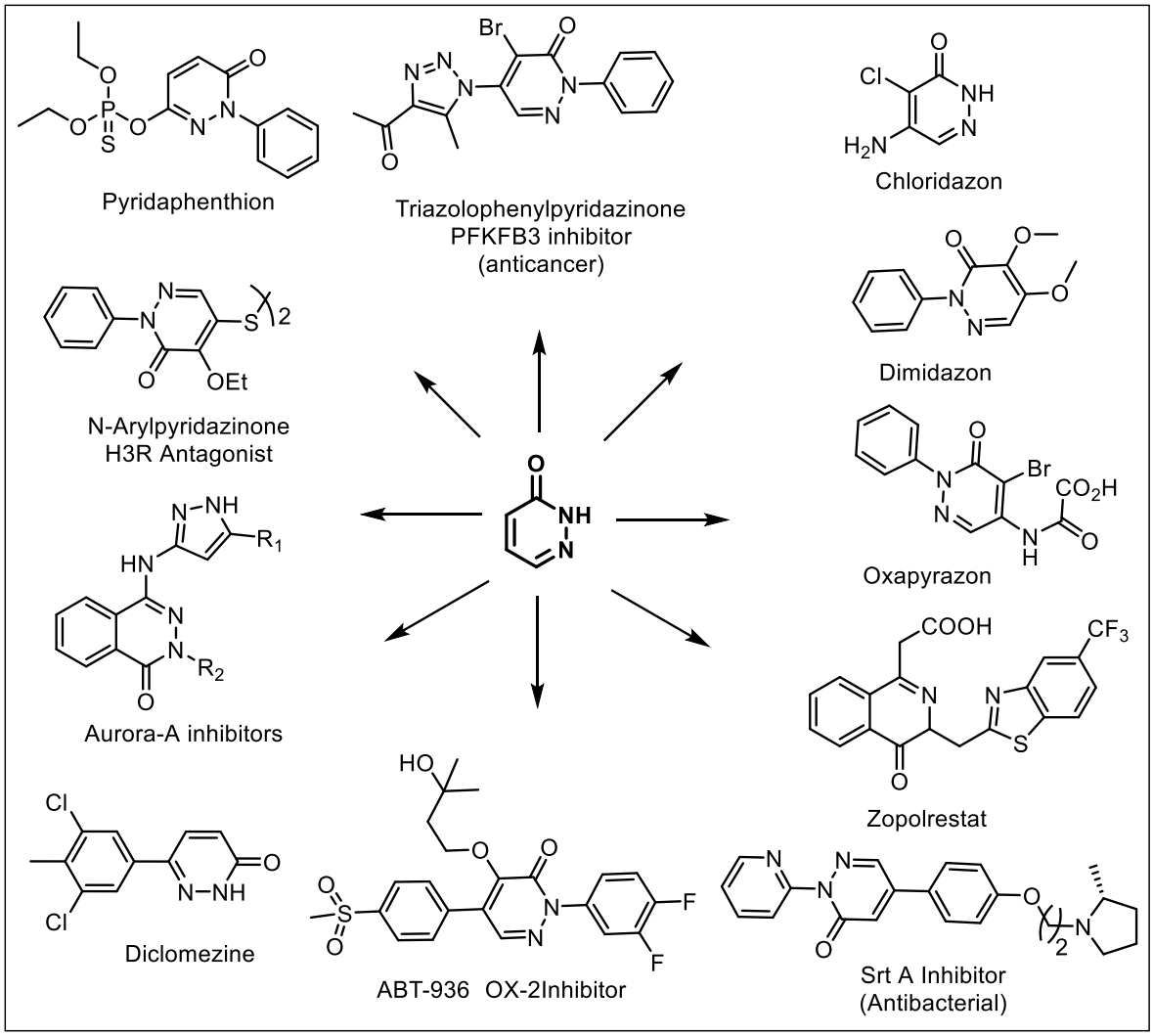
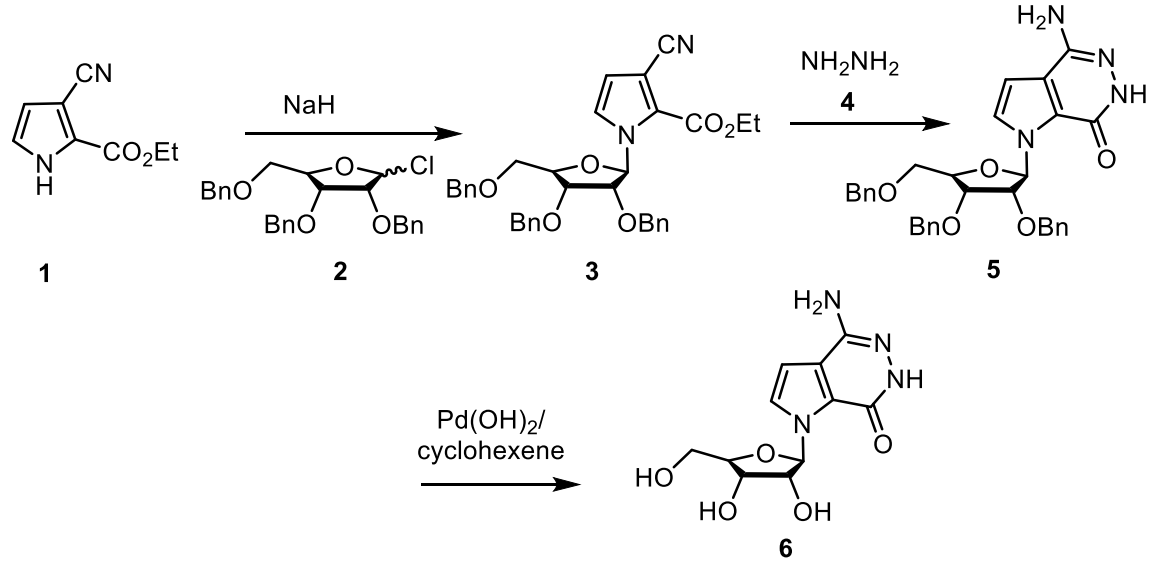


Figure 5.1 Bioactive compounds containing the pyridazinone scaffold

Due to their broad and powerful pharmacologic activities, the syntheses of polysubstituted pyrrolo-[2, 3-*d*]pyridazinone compounds have attracted continuous interest from both organic and medicinal chemists. The most frequently used strategy for the construction of a pyridazinone ring is based on the condensation of a hydrazine or substituted hydrazines with γ-carbonyl acids or their derivatives.[41-54] Another method for the formation of pyridazinones is to utilize a hydrazone of a 1, 2-dicarbonyl compound as a substrate to react with ethyl cyanoacetate,[55-56] phosphonium ylides of carboxylates,[57-58] 2-benzylidene cyanoacetate, or 2-benzylidene malononitrile,[59] followed by intramolecular cyclization. Several other methods for the synthesis of this kind of nitrogen heterocycles are described in the literature which are sometimes prepared

from aryldiazonium salts.[60-72] Other methods such as palladium-catalyzed cross coupling reactions involving aryldiazonium salts and heteroaryltrifluoroborate using water as a solvent was developed by Roglans *et al.* The same reaction was also tested without the palladium catalyst and found that the same heterocycles were obtained.[73-74] However these protocols have disadvantages, such as the increased number of reaction steps and subsequent purification processes, thus increasing the total time and cost of the synthesis. Precedent for such a transformation is limited; although several number of novel methodologies have been established to generate diverse substituted pyrrolo-pyridazinones ring systems having tremendous applications in drug design and discovery from last few years. Some of the important methodologies established are described as below.

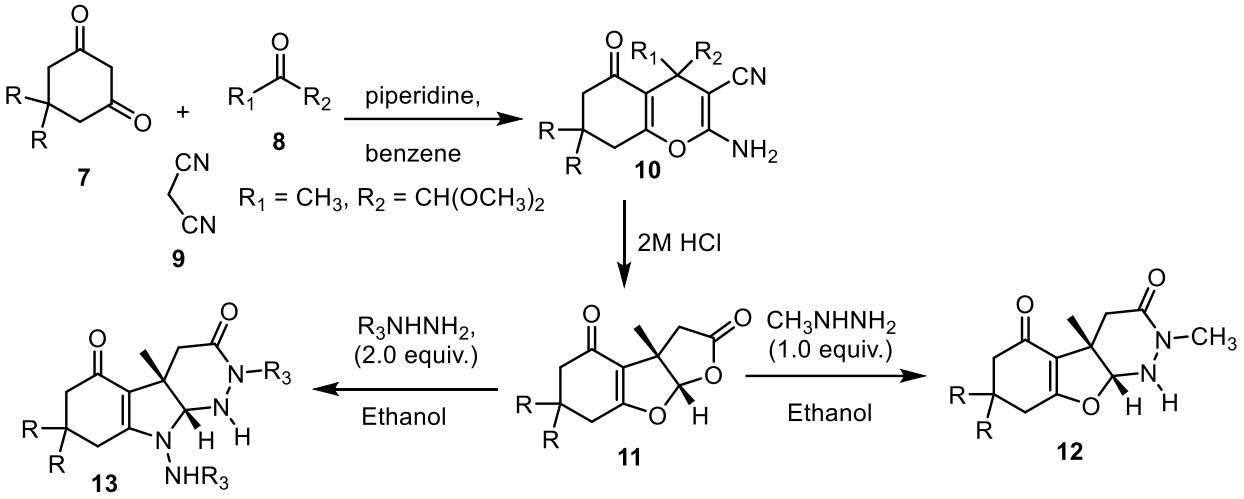
For example, Townsend and coworkers attempted the synthesis of 4-amino-l-*β*-D-ribofuranosylpyrrolo-[2,3-*d*]pyridazin-7(6*H*)-one (**6**) from the reaction of ethyl 3-cyano-1-*β*-D-ribofuranosylpyrrole-2-carboxylate (**3**)and hydrazine (**4**).This pyrrolo-[2,3-*d*]pyridazin-7(6*H*)-one structure of (**6**) was established *via* a three-step conversion as shown in (**Scheme 5.1**). They first elected to use 2, 3, 5-tri-O-benzyl-l-*β*-D-ribofuranosyl chloride (**2**)[75]as the sugar for the glycosylation procedure with the pyrrole (**1**) for further transformations in the synthetic sequence.[76]



Scheme 5.1 Synthesis of 4-amino-l-β-D-ribofuranosylpyrrolo-[2, 3-*d*]pyridazin-7(6*H*)-ones

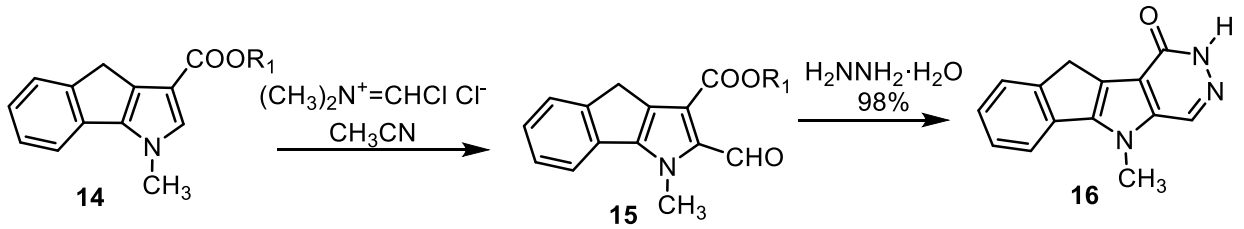
Okawara and co-workers reported the synthesis of fused pyrrole-pyridazinones (**13**) and furo-pyridazinones (**12**) from 4-methyl-4-methoxymethypyrans (**10**), prepared from cyclohexane-1,3-

diones (**7**), pyruvaldehyde dimethylacetal (**8**) and malononitrile (**9**), are subjected to hydrolysis with HCl to give fused furfuranones (**11**) which are treated with different hydrazines to give two different products as shown in (**Scheme 5.2**).[77]



Scheme 5.2 Synthesis of fused pyrrolo-pyridazinones and furopyridazinones

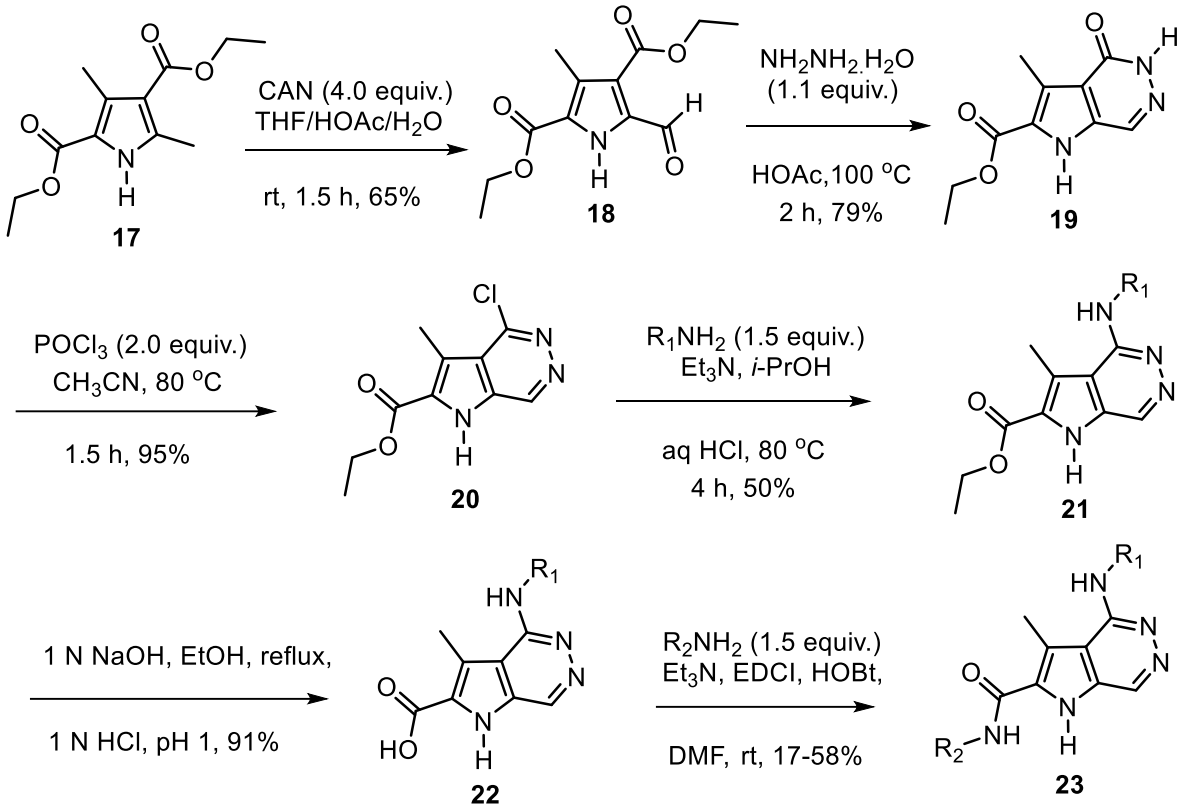
Pinna *et al.* investigated the novel synthesis of pyrrolo-[2,3-*d*]pyridazinones (**16**) from the common strategy that is, formylation of the appropriate esters (**14**) with Vilsmeier's reagent in acetonitrile to afford the corresponding 2-formyl derivatives (**15**) which were finally condensed with hydrazine to give the desired compounds (**16**) as shown in (**Scheme 5.3**).[78]



Scheme 5.3 Synthesis of pyrrolo-[2, 3-*d*]pyridazin-4-one derivatives

Tang *et al.* reported a series of novel pyrrolo-pyridazine derivatives showing significant HER-2 inhibitor activity. These compounds selectively inhibited HER-2 kinase activity at low nanomolar concentrations (IC_{50} of 4 µM).[79] As shown in (**Scheme 5.4**), the reaction of pyrrole diester (**17**) with ceric ammonium nitrate (CAN) afforded pyrrole aldehyde (**18**),[80] which underwent a cyclization with hydrazine hydrate in acetic acid to give pyrrolo-[2,3-*d*]pyridazin-4-one (**19**). The pyrrolo-[2,3-*d*]pyridazin-4-one was transformed into the 4-chloro-pyridazine derivative (**20**) upon treatment with $POCl_3$. Acid catalyzed displacement of the chloride with the

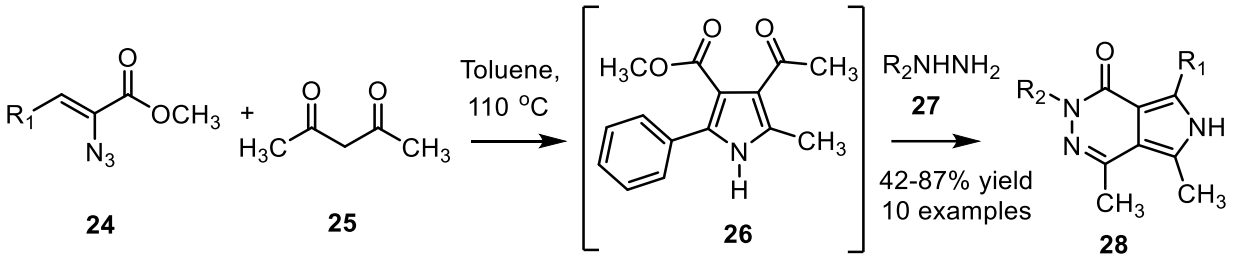
appropriate aniline was performed in isopropanol to give (**21**). Saponification of (**21**) yielded the product (**22**) which was further followed by coupling with different amines to give compound (**23**).



Scheme 5.4 Synthesis of pyrrolo-pyridazine derivatives

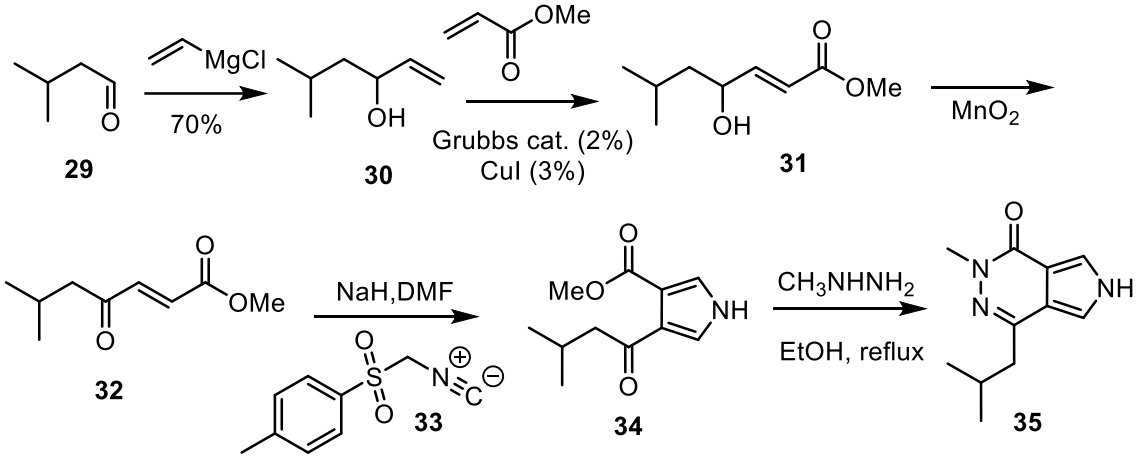
Bonacorso and coworkers demonstrated a new one-pot method, for the synthesis of polysubstituted pyrrolo-[3,4-*d*]pyridazinone derivatives (**28**) and their corresponding analogs. The one-pot operation involves cascade reactions performed in the same media (**Scheme 5.5**)[81]

The thermal *in situ* pyrrole formation (**26**) by the reaction of vinyl azides (**24**) with 1,3-dicarbonyl compounds (**25**), via the 1,2-addition of 1,3-dicarbonyl compounds to 2*H*-azirine intermediates. The nucleophilic addition of hydrazines (**27**) to the ketone group present in the pyrroles previously formed (**26**), followed by intramolecular cyclization with the bordering ester, which furnishes the respective pyrrolo-[3,4-*d*]pyridazinones (**28**), which are substituted at the different positions of pyrrole and pyridazinone rings. All transformations occur in a two-step one-pot methodology, and a series of new biologically active compounds were obtained with high yields (42–87%).



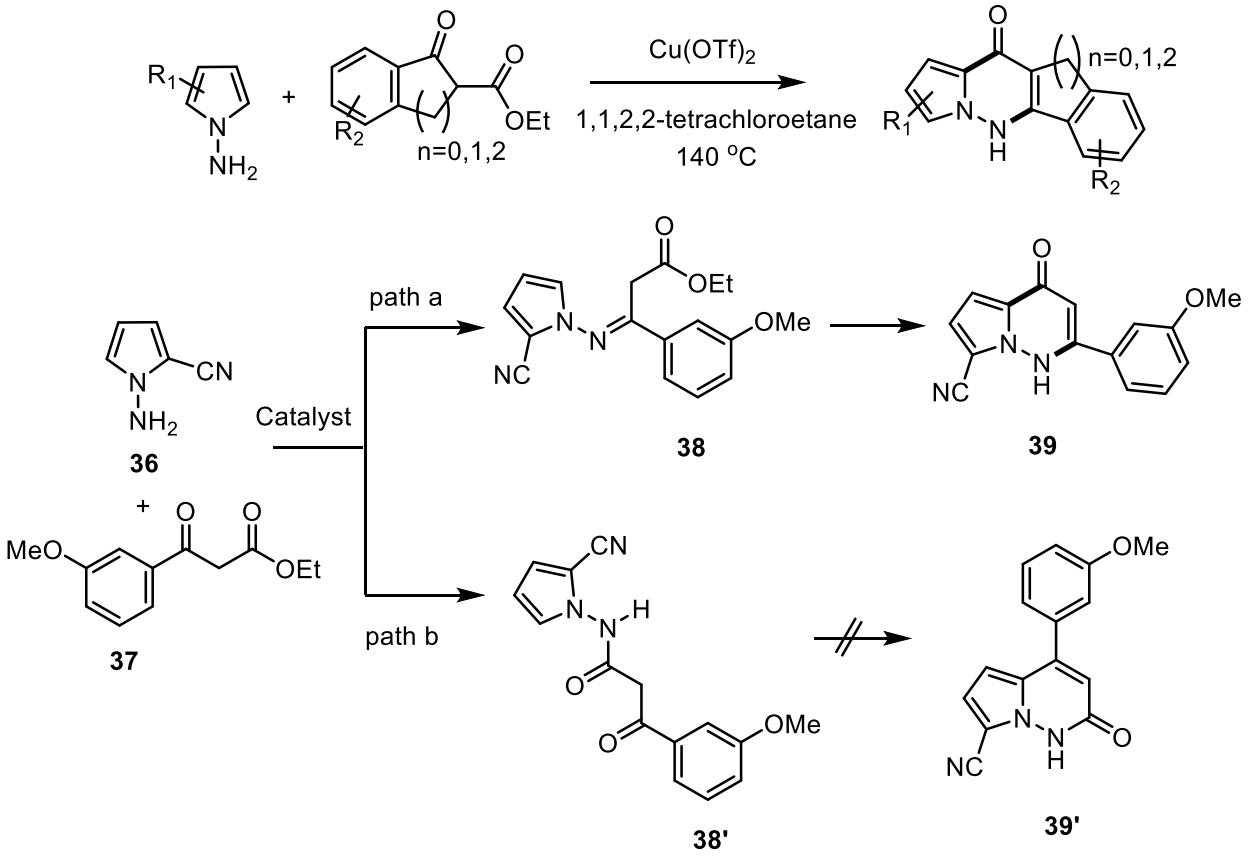
Scheme 5.5 One-pot formation of pyrrolo-[3, 4-*d*] pyridazinones

Recently, Bannister and coworkers reported a Grubbs cross-metathesis strategy to prepare keto ester (**31**), which is further used for the synthesis of substituted pyrrolo-[3, 4-*d*] pyridazin-1-one (**35**), the core scaffold of several pyridazinone based inhibitors (**Scheme 5.6**)[82] The efficiency of the process gave access to a number of substituted analogs of interest as possible antitumor agents.



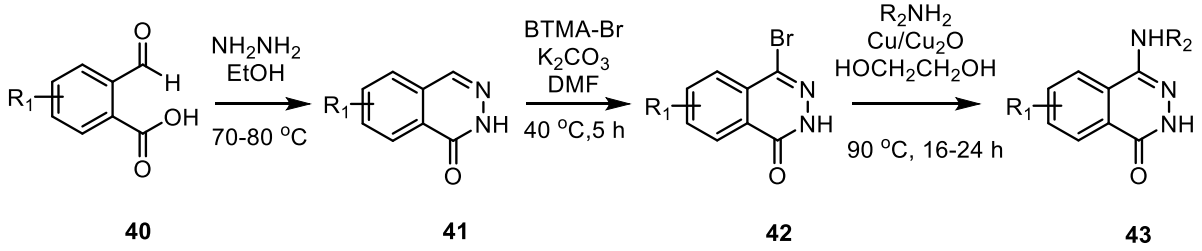
Scheme 5.6 Synthesis of keto ester and fused pyrrole-pyridazinone

Yang *et al.* investigated one-pot copper (II) catalyzed the tandem synthesis of 2-substituted pyrrole-[1,2-*b*]pyridazin-4-(1*H*)-ones (**39**) from *N*-amino pyrrole (**36**) and ethyl-3-(3-methoxyphenyl)-3-oxopropanoate (**37**) and hence desired product (**39**) was obtained in a moderate yield. This tandem reaction involves a Conrad-Limpach-type reaction, including the thermal condensation of *N*-amino pyrrole with the carbonyl group of *β*-oxo esters followed by the cyclization of Schiff base intermediates (**38**). Toward this goal, they developed first applied copper (II) as a catalyst in the Conrad-Limpach reaction to furnish pyrrolo-[1,2-*b*]pyridazin-4(1*H*)-ones in a one-pot procedure at a lower temperature of 140 °C (**Scheme 5.7**).[83] The corresponding products could be converted directly into diverse pyrrole-[1,2-*b*]pyridazine for drug discovery and materials science.



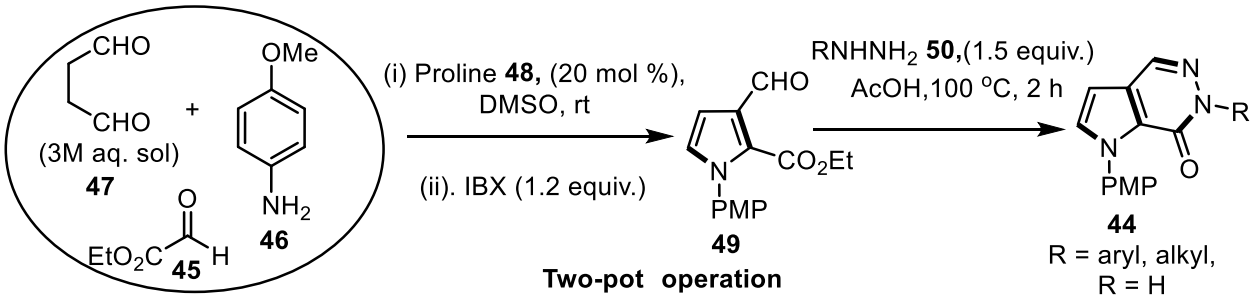
Scheme 5.7 Conrad-Limpach reaction for the synthesis of pyrrolo-[1,2-*b*]pyridazin-4(1*H*)-ones

Very recently, Krishnananthan and coworkers described an efficient regioselective synthesis of substituted 4-alkylamino and 4-arylaminophthalazin-1(2*H*)-ones (**43**) by the reaction of 2-formylbenzoic acids (**40**) with hydrazine followed by further selectively bromination of (**41**) at the 4-position to give 4-bromophthalazin-1(2*H*)-ones (**42**). Subsequent metal-catalyzed C–N coupling of (**42**) with amines would give the desired 4-alkylamino and 4-arylaminophthalazin-1-(2*H*)-ones (**43**) in overall good yields in all most all cases (**Scheme 5.8**).[84]



Scheme 5.8 Regioselective synthesis of aminophthalazin-1-(*2H*)-ones

Despite all the studies, papers and patents mentioning the numerous biological activities of this class of compounds, no method have been developed so far for the synthesis of pyrrolo-[2, 3-*d*]pyridazinone ring systems as far as we know. Based on our recent success in the organocatalytic synthesis of nitrogen-containing core skeleton,[85-88] we speculated that a new simple and mild method for the preparation of *N*-aryl pyrrolo-[2,3-*d*]pyridazinones (**44**) could be set up directly from (i) the in situ imine formation from ethyl glyoxalate (**45**), and *p*-anisidine (**46**); (ii) the reaction of imine prepared in situ with succinaldehyde (**47**) which acts as 1,3-carbon *donor-acceptor* (D-A) precursor, through [3+2] direct Mannich annulations followed by IBX mediated aromatization to 3-formylpyrrole intermediates (**49**); (iii) the nucleophilic addition of hydrazines (**50**), to the formyl group present in the pyrroles previously formed, followed by intramolecular cyclization with the bordering ester, under mild conditions that led to formation of diverse pyridazinone derivatives *via* multi-component tandem cyclization in two-pot process with good to excellent yields in almost all the cases (**Scheme 5.9**).



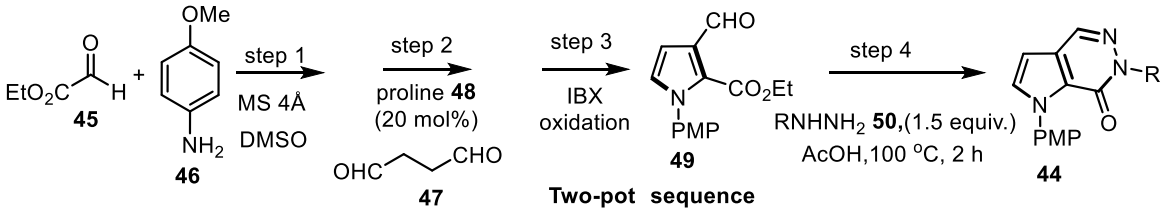
Scheme 5.9 Direct approaches to fused pyrrolo-[2, 3-*d*]pyridazin-7-ones from succinaldehyde

5.2 Results and Discussion

During our experimental studies, we initially carried out all the steps of one-pot multi-component/domino-reaction at room temperature with proline **48** (20 mol %) in DMSO as preferred solvent. Interestingly, this proline catalyzed direct Mannich reaction/cyclization between succinaldehyde (**47**) and in situ generated imine from ethyl glyoxalate (**45**) and *p*-anisidine (**46**), followed by IBX-oxidation as one-pot domino sequence does not gave any of the products (**49** and **44**) (**entry 1, Table 5.1**). We did not alter the amine catalyst or solvent as they turn out to be best in our previous studies for first step. However, by changing the reaction temperature at individual steps, we could obtain our intermediate pyrrole product (**49**) along with

the final desired product (**44**) in lesser yield when condensed with phenyl hydrazine (**50**) in the same pot (**entry 2, 3 Table 5.1**). A further change in the reaction conditions that is addition of an equimolar volume of AcOH as solvent in the same vessel (**entry 4, Table 5.1**), resulted in formation of the final desired product (**44**) upto 50 % yield showing that AcOH is necessary for such a process. Thus, we choose to perform this in two-pot protocol of sequential multi-component amine catalyzed [3+2] annulation/IBX oxidation/acid mediated condensation through preferred conditions using only AcOH as solvent for step 4 (**entry 5, Table 5.1**).The yield was further increased to 70%, although with an increased reaction temperature to 100 ^{o}C while decreasing the reaction time to 3 hours increases the reaction yields perhaps, avoiding the decomposition of the reaction products **(entry 6, Table 5.1)**. Hence, the optimized reaction conditions **(entry 7, Table 5.1)** was adopted for further studies of the reaction scope while changing the concentration of phenyl hydrazine (**50**).

Table 5.1 Optimized reaction condition for pyrrolo-[2, 3-*d*]pyridazin-7-one synthesis **44a**



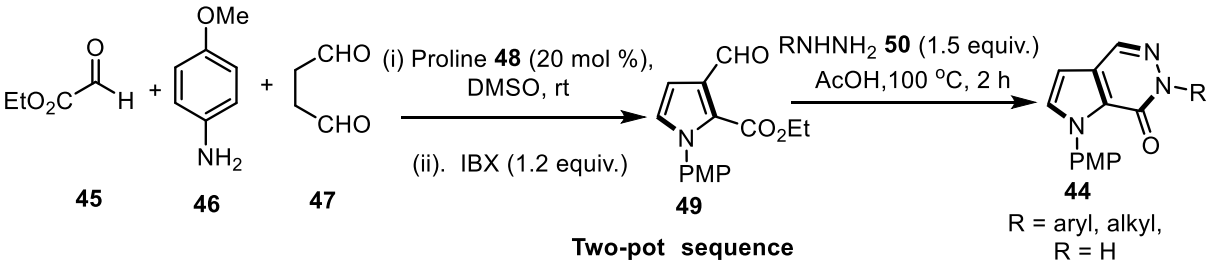
Entry	Conditions[a]				Yield (%)[b]
	First-pot			Second pot	
	Step 1	Step 2	Step 3	Step 4	
1	DMSO, rt, 3 h	rt, 6 h	IBX, rt, 3 h	$RNHNH_2$, rt, 6 h	n.r
2	DMSO,rt, 3 h	rt, 6 h	IBX, 50 ^{o}C, 3 h	$RNHNH_2$, 50 ^{o}C, 6h	20
3	DMSO,rt, 3 h	rt, 6 h	IBX, 70 ^{o}C, 3 h	$RNHNH_2$, 70 ^{o}C, 6 h	35
4[c]	DMSO,rt, 3 h	rt, 6 h	IBX, 70 ^{o}C, 3 h	AcOH, $RNHNH_2$, 80 ^{o}C, 6 h	50
5[c]	DMSO,rt, 3 h	rt, 6 h	IBX, 70 ^{o}C, 3 h	$RNHNH_2$, 100 ^{o}C, 6 h	60
6[c]	DMSO,rt, 3 h	rt, 6 h	IBX, 70 ^{o}C, 3 h	AcOH, $RNHNH_2$, 100 ^{o}C, 3 h	70
7[d]	**DMSO,rt, 3 h**	**rt, 6 h**	**IBX, 70 ^{o}C, 3 h**	**AcOH, $RNHNH_2$, 100 ^{o}C, 3 h**	**75**
8[e]	DMSO,rt, 3 h	rt, 6 h	IBX, 70 ^{o}C, 3 h	AcOH, $RNHNH_2$, 100 ^{o}C, 3 h	75

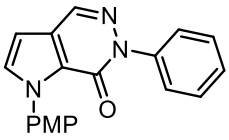
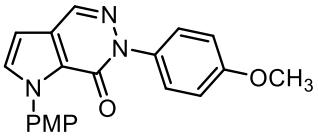
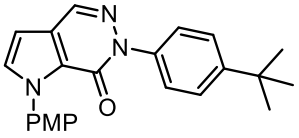
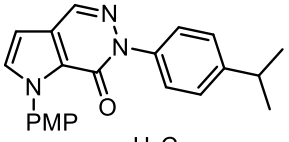
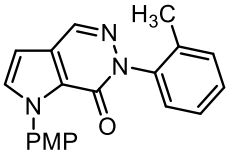
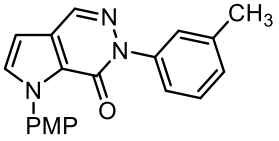
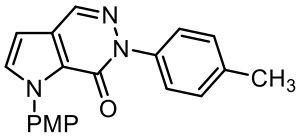
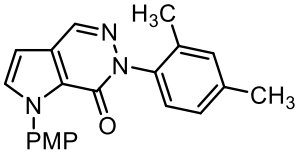
[a]Unless otherwise indicated, the reaction was carried out with: (step 1); **45** (0.3 mmol, 30 mg), **46** (0.3 mmol, 37 mg), DMSO (3.0 mL) (step 2); succinaldehyde **47** (0.6 mmol, 52 mg), Proline

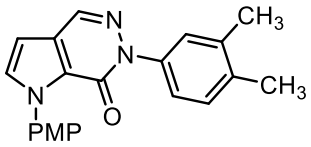
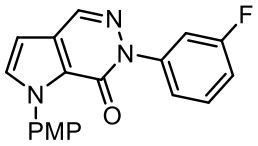
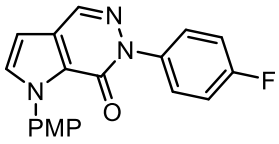
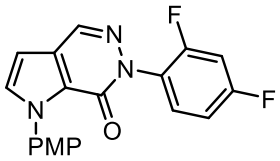
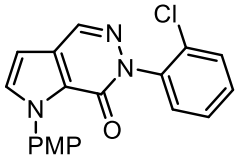
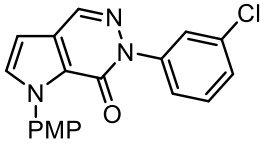
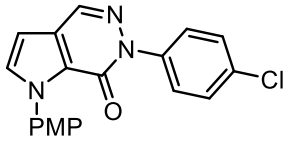
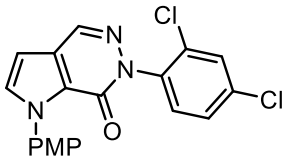
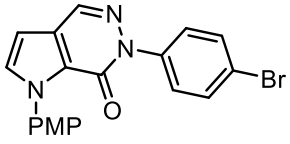
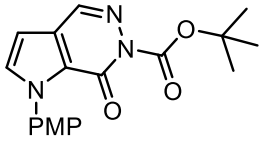
48 (20 mol %), (step 3); IBX (120 mol %), (step 4); [c]**50** (0.3 mmol, 95 mg), AcOH (3.0 mL) at 100 °C was added after IBX oxidation. [b]The yields are of the isolated products. [d]($RNHNH_2$) **50** (0.45 mmol, 142 mg), and [e]($RNHNH_2$) **50** (0.6 mmol, 187 mg), were added during second step.

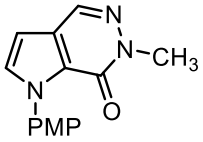
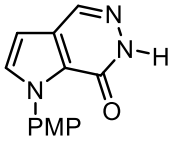
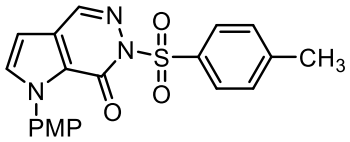
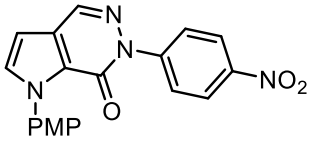
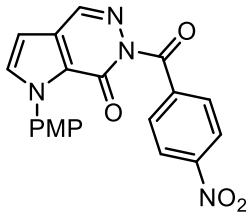
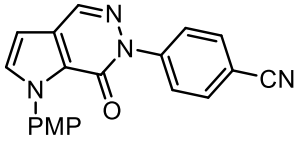
With respect to the compound (**49**) having aldehyde and ester functionality obtained from amine catalyzed direct Mannich reaction/cyclization between succinaldehyde (**47**) and in situ generated imine from ethyl glyoxalate (**45**) and *p*-anisidine (**46**), followed by IBX-oxidation sequence reacted with different hydrazine substrates (**50**), we established the reaction conditions for this two-pot domino sequence to produce series of pyrrolo-[2,3-*d*]pyridazinone derivatives (**44**) with excellent yields (**Table 5.2, entries 1-20**). However, the hydrazines substituted by an electron-withdrawing group at *ortho* and *meta* positions gave desired products with lower yields **(entries 44g, 44i, 44j, Table 5.2).** Apart from that, *p*-substituted hydrazines gave products in good yields **(entries 44f, 44h, 44k, Table 5.2).** The lower chemical yield of product **44e** and **44l** derived from the dual substitution on the phenyl ring of hydrazine is probably due to the lower stability and steric crowding. It was found that the substitution pattern of hydrazines also influenced the outcome of the reaction, as 4-methoxyphenylhydrazine produced a higher yield (78%) of product **44b** than that of **44a** (75%). Due to the presence of bulky group on hydrazine moiety yield is further reduced to 70% as in the case of **(entry 44c, Table 5.2).** In comparison to the aromatic hydrazines, the reactions of aliphatic hydrazines produced lower yields of products **44s, 44t and 44u** (58%−64% yield) probably because the aliphatic hydrazines were less stable under the reaction conditions (**Table 5.2, entries 44s, 44t, and 44u**). We next examined the reaction with tosyl phenyl hydrazine, *p*-nitrophenyl hydrazines, *p*-nitrophenylhydrazide and *p*-nitrilephenyl hydrazines. It was found that only condensation product was observed but not the desired cyclized compound. This was probably attributable to the much weaker nucleophilicity of these hydrazines in comparison to other *N*-arylhydrazines (**Table 5.2, entries 44v-44y**).

Table 5.2 Substrate scope towards the synthesis of pyrrolo-[2,3-*d*]pyridazin-7-one (**44**)



Entry	R	Product	44	% Yield[b]
1	C_6H_5		**44a**	75
2	4-OCH_3-C_6H_4		**44b**	78
3	4-C-$(CH_3)_3$-C_6H_4		**44c**	70
4	4-CH-$(CH_3)_2$-C_6H_4		**44d**	72
5	2-CH_3-C_6H_4		**44e**	62
6	3-CH_3-C_6H_4		**44f**	66
7	4-CH_3-C_6H_4		**44g**	72
8	2,3-$(CH_3)_2$-C_6H_4		**44h**	60

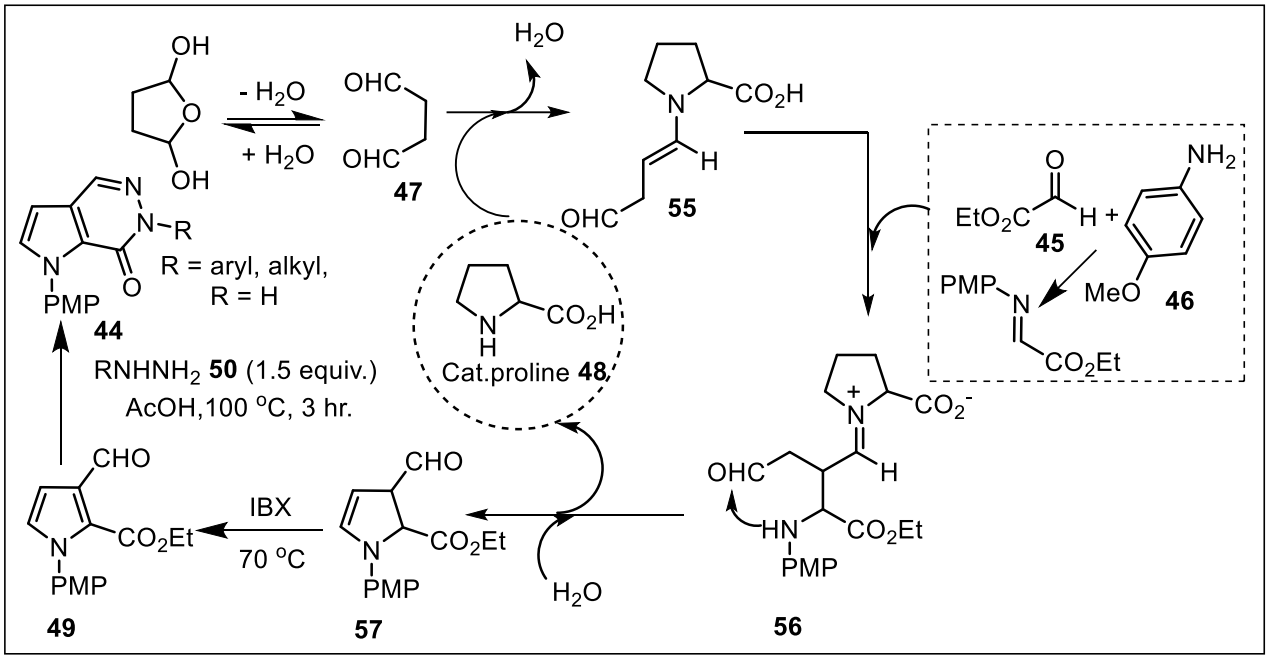
Entry	R	Product	44	% Yield[b]
9	2,3-$(CH_3)_2$-C_6H_4		**44i**	63
10	3-F-C_6H_4		**44j**	65
11	4-F-C_6H_4		**44k**	70
12	2,4-$(F)_2$-C_6H_4		**44l**	64
13	2-Cl-C_6H_4		**44m**	65
14	3-Cl-C_6H_4		**44n**	75
15	4-Cl-C_6H_4		**44o**	71
16	2,4-$(Cl)_2$-C_6H_4		**44p**	60
17	4-Br-C_6H_4		**44q**	70
18	^{t}BuOCO		**44r**	62

Entry	R	Product	44	% Yield[b]
19	CH_3		**44s**	64
20	H		**44t**	58
21	tosyl		**44u**	n.r
22	4-NO_2-C_6H_4		**44v**	n.r
23	4-NO_2-CO-C_6H_4		**44w**	n.r
24	4-CN-C_6H_4		**44x**	n.r

[a]Unless otherwise indicated, the reaction was carried out with (i) **45** (0.3 mmol, 30 mg), **46** (0.3 mmol, 37 mg), DMSO (3.0 mL) (ii) succinaldehyde **47** (0.6 mmol, 52 mg), Proline **48** (20 mol %), (iii) IBX (120 mol %) (iv) ($RNHNH_2$) **50** (0.45 mmol, 142 mg), [b]The yields are of the isolated products. [c]AcOH (3.0 mL) at 100 °C was added after IBX oxidation in next step.

Based on our initial study and literature precedents on proline-catalyzed Mannich reaction, the following stepwise mechanism is proposed to account for this reaction. As shown in (**Scheme 5.10**), the *in situ* generated enamine (**55**), generated from succinaldehyde (**47**) and proline, reacts

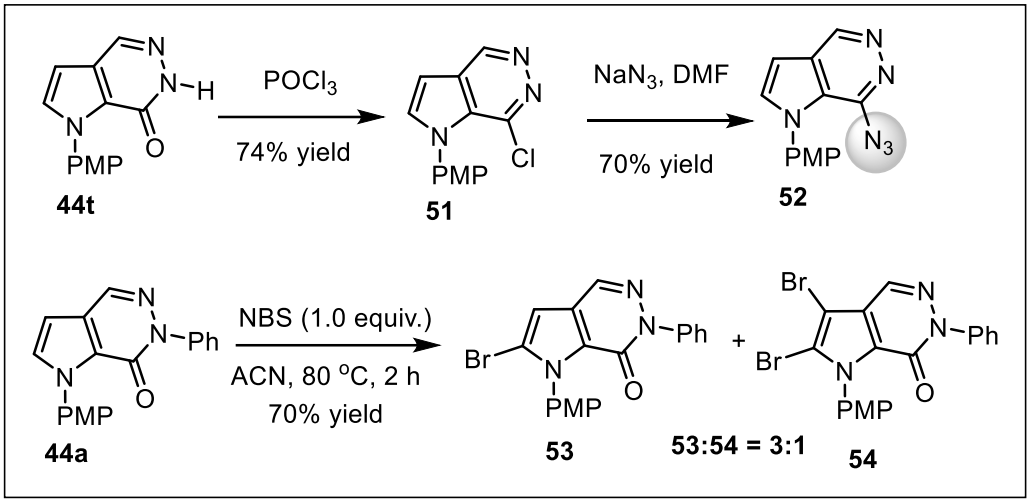
with *N*-PMP ethyl glyoxalate imine derived from ethyl glyoxalate (**45**) and *p*-anisidine (**46**) *via* a direct Mannich reaction to produce (**56**). The intermediate (**56**) undergoes intramolecular cyclization to enamine (**57**) with the simultaneous regeneration of proline. Enamine (**57**) underwent IBX mediated oxidative aromatization to afford the ethyl 3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (**49**) which undergoes nucleophilic addition of hydrazines (**50**) on the formyl functionality of the intermediate compound and further intramolecular cyclization with the bordered ester group present in the compound producing desired product in the form of pyrrolo-[3, 2-*d*] pyridazin-7(6*H*)-one (**44**).



Scheme 5.10 Mechanism for two steps synthesis of pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one

However, the present cycloaddition process could be easily carried out to produce versatile scaffolds such as pyrrolo-azido pyridazinone (**52**) and mono-bromopyrrolo-pyridazinone (**53**) and dibromopyrrolo-pyridazinone (**54**) derivatives as shown in (**Scheme 5.11**).[89-93] The compound (**44t**) was treated with $POCl_3$ at 80 °C resulting 4-chloro-pyridazine intermediate (**51**) which upon treatment with NaN_3 in DMF gave product (**52**) in good yields and compound (**44a**) upon treatment with *N*-bromosuccinimide (NBS) in acetonitrile at 80 °C resulting compound (**53**) and (**54**) in 3: 1 ratio as determined by ^{1}HNMR. Notably, these compounds

constitute essential subunits in many pharmaceutically important compounds and have also found applications in material synthesis and medicinal chemistry.



Scheme 5.11 Synthesis of pyrrolo-azido-pyridazinone, and bromopyrrolo-pyridazinones

5.3 Conclusions

In summary, we have developed a convenient method for the synthesis of a structurally unique series of substituted pyrrolo-[2, 3-*d*]pyridazinones **44**. The in situ 3-formylpyrrole **43** formation *via* direct Mannich cyclization cascade process from imine derived from ethyl glyoxalate **40** and *p*-anisidine **41** with the mutual combination of succinaldehyde **42**, followed by the nucleophilic addition of substituted hydrazines and then intramolecular cyclization generates the pyrrolo-[2, 3-*d*]pyridazinones **44** in a versatile new way, without the need for intermediate isolation and further purification steps. Despite some limitations with the reactivity of the hydrazine compounds containing electron withdrawing groups such as ($–NO_2$, –CN), tosyl hydrazines and acyl hydrazides, the aforementioned cascade protocol was applicable to a range of substrates, providing new compounds with high yields (58–78%), thus demonstrating the generality of this methodology. Experimental results suggest that AcOH might play a critical role in the final step for the synthesis of desired compound **44** which constitute a versatile scaffold for the synthesis of pyrrolo-azido pyridazinone and bromo-pyrrolo-pyridazinone derivatives.

5.4 General Experimental Methods

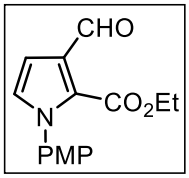
All reactions under standard conditions were monitored by thin-layer chromatography (TLC) on SiO_2 gel F-254 plates. Unless otherwise noted all reactions have been carried out with distilled and dried solvents. Oven (120 °C) dried glassware were used. All work up and purification were carried out with reagent grade solvents in the air. 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 on a BRUKER-AV400 (400 MHz and 75 MHz) spectrometer 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. Infrared (FT-IR) spectra were recorded on an ABB Bomen MB 3000 FTIR Spectrophotometer system using KBr pellets.

5.5 General procedure for the synthesis of pyrrolo-[2, 3-*d*]pyridazin-7(6*H*)-one (44)

Succinaldehyde (**47**) (0.3 mL, 0.6 mmol, 52 mg) was added to a mixture of *in situ N*-PMP aldimine from ethyl glyoxalate (**45**), (0.3 mmol, 30 mg), *p*-anisidine (**46**), (0.3 mmol, 37 mg) and L-proline **48** (7.0 mg, 0.06 mmol) in DMSO (3.0 mL) at room temperature. The reaction mixture was stirred at room temperature until the aldimine was consumed as monitored by TLC. Further, in the same pot IBX (100 mg, 0.36 mmol, 1.2 equiv.) was added and the reaction mixture was stirred and heated at 70 ^{o}C for 3 h and cooled to room temperature. The reaction was quenched with a saturated $NaHCO_3$ solution (3 mL) and extracted with ethyl acetate (6 mL) three times. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue of pyrrole 3-carbxaldehydes (0.3 mmol), (**49**) was dissolved in AcOH (3.0 mL) and then further a hydrazine (**50**) (0.45 mmol, 142 mg, 1.5 equiv.) was added into the reaction vessel and refluxed at 100 ^{o}C for 3 hours. The reaction was quenched with a saturated $NaHCO_3$ solution (10 mL) and extracted with ethyl acetate (15 mL) twice and combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification through silica gel column chromatography by eluting the mixture of EtOAc/ hexane, gave pyrrolo-[3, 2-*d*] pyridazin-7(6*H*)-one (**44**) with 58-

78% yields. In some of the cases, we obtained only condensation product instead of the desired one. The pure products were characterized based upon their spectroscopic data.

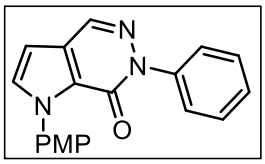
5.6 Analytical data of ethyl 3-formyl-1-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (49)



(Yellow viscous liquid, 61 mg, yield 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, *J* = 7.2 Hz, 7.1 Hz, 3H), 3.85 (s, 3H), 4.20-4.25 (q, 2H), 6.82 (d, *J* = 2.8 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 7.21 (d, *J* = 8.9 Hz, 2H), 10.45 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.95, 55.45, 61.08, 108.81, 113.93 (2C), 127.26 (2C), 129.15, 129.23, 130.35, 132.65, 159.58, 159.61, 188.18; IR (KBr)/cm^{-1} 2980, 1728, 1672, 1514, 1379, 1251, 1116; HRMS (ESI):Calcd for $C_{15}H_{15}NO_4$ (M-H$^+$) 274.1079; Found 274.1083.

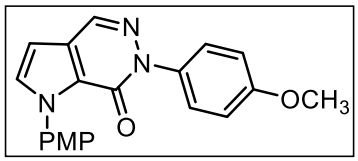
5.7 Analytical data of synthesized compounds (44a-44t)

1-(4-methoxyphenyl)-6-phenyl-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44a)



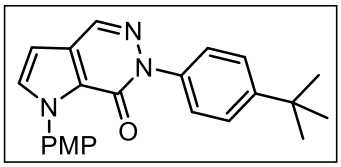
(Dark brown solid; M.P =156-158 °C, 71 mg, yield 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.57 (d, *J* = 7.4 Hz, 2H), 7.43 (d, *J* = 7.5 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 2.9 Hz, 1H), 6.95 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 2.9 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.32, 154.08,141.89, 134.29, 132.70, 131.59, 128.54 (2C), 127.52, 127.37(2C), 126.36 (2C), 125.95, 125.68, 113.77 (2C), 103.37, 55.50; IR (KBr)/cm^{-1} 2924, 1736, 1666, 1605, 1512, 1296, 1250, 1119, 1026; HRMS (ESI): Calcd for $C_{19}H_{15}N_3O_2$ (M-H$^+$) 318.1243; Found 318.1248.

1, 6-bis-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44b)



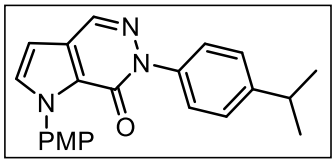
(Red solid; M.P =169-172 °C, 81 mg, yield 78%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.47 (d, *J* = 9.0 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 3.0 Hz, 1H), 6.95 (d, *J* = 3.1 Hz, 2H), 6.93 (d, *J* = 3.2 Hz, 2H), 6.61 (d, *J* = 3.0 Hz, 1H), 3.83 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.30, 158.77, 154.16, 134.99, 134.05, 132.60, 131.62, 127.47 (2C), 127.35 (2C), 125.98, 125.67, 113.81(2C), 113.75 (2C), 103.31, 55.50, 55.49; IR (KBr)/cm^{-1} 2962, 1666, 1612, 1512, 1443, 1250, 1180, 1034, 833; HRMS (ESI): Calcd for $C_{20}H_{17}N_3O_3$ (M-H$^+$)348.1349; Found 348.1355.

6-(4-*tert*-butylphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44c)



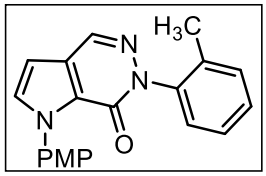
(Light yellow solid; M.P =162-164 °C, 78 mg, yield 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.48 (d, *J* = 8.9 Hz, 2H), 7.43 (d, *J* = 8.9 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 3.0 Hz, 1H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.61 (d, *J* = 3.0 Hz, 1H), 3.83 (s, 3H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.20, 154.08, 150.46, 139.16, 134.17, 132.58, 131.53, 127.35 (2C), 125.76 (2C), 125.56 (2C), 122.84, 114.82, 113.67 (2C), 103.34, 55.49 (3C), 34.56, 31.27 ; IR (KBr)/cm^{-1} 2978, 1720, 1674, 1512, 1373, 1250, 1165; HRMS (ESI): Calcd for $C_{23}H_{23}N_3O_2$ (M-H$^+$) 374.1869; Found 374.1873.

6-(4-*iso*-propylphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44d)



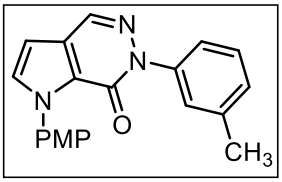
(Brown solid, M.P =158-160 °C, 76 mg, yield 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.47 (d, *J* = 8.5 Hz, 2H), 7.40 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 3.0 Hz, 1H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.61 (d, *J* = 3.0 Hz, 1H), 3.82 (s, 3H), 2.92 (dt, *J* = 13.8, 6.9 Hz, 1H), 1.25 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.22, 154.07, 148.26, 139.52, 134.11, 132.57, 131.56, 127.34 (2C), 126.58 (2C), 126.13 (2C), 125.90, 125.65, 113.69 (2C), 103.31, 55.48, 33.85, 23.94 (2C); IR (KBr)/cm^{-1} 2955, 1659, 1582, 1513, 1250, 1119, 833; HRMS (ESI): Calcd for $C_{22}H_{21}N_3O_2$(M-H$^+$)360.1712; Found 360.1716.

1-(4-methoxyphenyl)-6-o-tolyl-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44e)



(Light yellow solid, M.P =156-158 °C, 61 mg, yield 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 3.0 Hz, 1H), 7.28 (s, 3H), 6.94 (d, *J* = 9.0 Hz, 3H), 6.64 (d, *J* = 3.0 Hz, 1H), 3.81 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.25, 153.98, 140.93, 139.28, 135.31, 134.11, 132.49, 130.82, 128.63, 128.21, 127.61, 127.29 (2C), 126.65, 125.88 , 113.74 (2C), 103.46, 55.51, 22.68; IR (KBr)/cm^{-1} 2962, 1666, 1512, 1443, 1296, 1250, 1180, 1026, 903, 808; HRMS (ESI): Calcd for $C_{20}H_{17}N_3O_2$ (M-H$^+$) 332.1400; Found 332.1405.

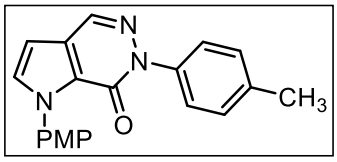
1-(4-methoxyphenyl)-6-m-tolyl-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44f)



(Light brown solid; M.P =171-173 °C, 65 mg, yield 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.36 (s, 1H), 7.33 (d, *J* = 5.8 Hz, 1H), 7.30 (dd, *J* = 5.3, 2.3 Hz, 2H), 7.14 (d, *J*

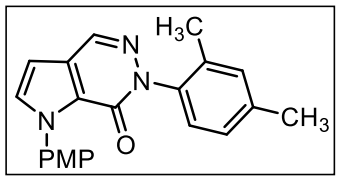
= 6.9 Hz, 1H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 2.9 Hz, 1H), 3.83 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.24, 154.08, 141.72, 138.53, 134.20, 132.68, 131.54, 128.46, 128.44, 127.36 (2C) 126.94, 125.88, 125.67, 123.51, 113.72 (2C), 103.38, 55.51, 21.34; IR (KBr)/cm^{-1} 2962, 1666, 1612, 1512, 1296, 1250, 1034, 833; HRMS (ESI): Calcd for $C_{20}H_{17}N_3O_2$ (M-H$^+$) 332.1400; Found 332.1396.

1-(4-methoxyphenyl)-6-p-tolyl-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44g)



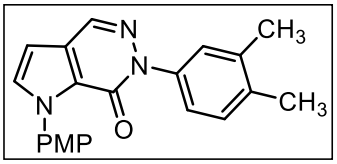
(Brown solid, M.P =160-162 °C, 71 mg, yield 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.43 (d, *J* = 8.3 Hz, 2H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 3.0 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 9.0 Hz, 2H), 6.61 (d, *J* = 3.0 Hz, 1H), 3.83 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.17, 154.03, 139.28, 137.31, 134.09, 132.57, 131.50, 129.07 (2C), 127.29 (2C), 126.03 (2C), 125.83, 125.61, 113.65 (2C), 103.29, 55.44, 21.06; IR (KBr)/cm^{-1} 3132, 2924, 1666, 1520, 1443, 1250, 1180, 825; HRMS (ESI): Calcd for $C_{20}H_{17}N_3O_2$ (M-H$^+$) 332.1400; Found 332.1408.

6-(2,4-dimethylphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44h)



(Dark brown solid, M.P = 165-167 °C, 62 mg, yield 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 3.0 Hz, 1H), 7.16 (d, *J* = 7.9 Hz, 1H), 7.05 – 7.10 (m, 2H), 6.93 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 3.0 Hz, 1H), 3.81 (s, 3H), 2.32 (s, 3H), 2.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.18, 154.08, 141.65, 138.41, 134.85, 134.03, 133.03, 132.44, 131.63, 131.45, 127.93, 127.28 (2C), 125.89, 121.35, 113.69 (2C), 103.44, 55.51, 21.11, 17.52; IR (KBr)/cm^{-1} 2924, 1666, 1512, 1443, 1381, 1250, 1026, 833; HRMS (ESI): Calcd for $C_{21}H_{19}N_3O_2$ (M-H$^+$) 346.1556; Found 346.1560.

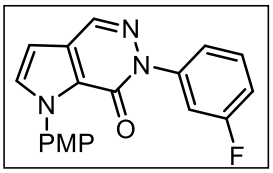
6-(3,4-dimethylphenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44i)



(Yellow solid, M.P =164-167 °C, 65 mg, yield 63%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.40 (d, *J* = 8.9 Hz, 2H), 7.31 (d, *J* = 2.2 Hz, 1H), 7.29 (d, *J* = 2.9 Hz, 1H), 7.27 (s, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 2.9 Hz, 1H), 3.82 (s, 3H), 2.26 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.17, 154.10, 141.56, 139.45, 136.91, 136.20, 134.06, 132.60, 131.51,

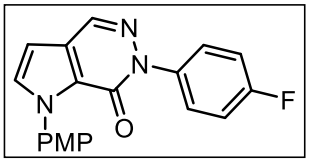
129.66, 127.32 (2C), 127.25, 125.67, 123.68, 113.66 (2C), 103.33, 55.47, 19.80, 19.43; IR (KBr)/cm^{-1}; HRMS (ESI): Calcd for $C_{21}H_{19}N_3O_2$ ($M-H^+$) 346.1556; Found 346.1551.

6-(3-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44j)



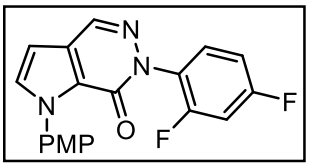
(White solid, M.P =166-168 °C, 65 mg, yield 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ; 8.29 (s, 1H), 7.41 – 7.44 (m, 1H), 7.37 – 7.40 (m, 3H), 7.34 – 7.37 (m, 1H), 7.30 (d, *J* = 2.9 Hz, 1H), 7.00 – 7.06 (m, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 2.9 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.34, 159.42, 153.97, 134.69, 132.92, 131.48, 129.58, 129.48, 127.36 (2C), 125.66, 122.00, 114.53, 114.36, 114.08, 113.83 (2C), 103.55, 55.52; IR (KBr)/cm^{-1} 2924, 1674, 1612, 1512, 1250, 1173, 1119, 1026, 833; HRMS (ESI): Calcd for $C_{19}H_{14}FN_3O_2$ ($M-H^+$) 336.1149; Found 336.1154.

6-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44k)



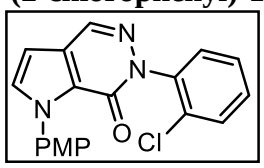
(Yellow solid, M.P =176-178 °C, 71 mg, yield 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.55 (dd, *J* = 9.0, 5.0 Hz, 2H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.30 (d, *J* = 2.9 Hz, 1H), 7.10 (t, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 9.0 Hz, 2H), 6.63 (d, *J* = 2.9 Hz, 1H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.83, 160.38, 159.35, 154.07, 137.80, 134.46, 132.84, 131.46, 128.16, 128.07, 127.34 (2C), 125.75, 115.45, 115.22, 113.77 (2C), 103.48, 55.51; IR (KBr)/cm^{-1} 2962, 1666, 1512, 1250, 1119, 1026, 833; HRMS (ESI): Calcd for $C_{19}H_{14}FN_3O_2$ ($M-H^+$) 336.1149; Found 336.1153.

6-(2, 4-difluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44l)



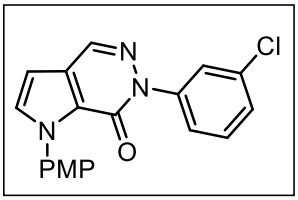
(Dark yellow pasty liquid, 67 mg, yield 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.42 – 7.46 (m, 1H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.32 (d, *J* = 3.0 Hz, 1H), 6.92 – 6.97 (m, 4H), 6.64 (d, *J* = 2.9 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.40, 153.82, 139.27, 134.95, 132.75, 131.33, 130.13 (d, *J* = 10.2 Hz), 128.82, 128.20, 127.25 (2C), 125.87, 125.44, 113.83 (2C), 111.47 (dd, *J* = 22.6, 3.8 Hz), 104.77 (dd, *J* = 26.4, 2.7 Hz), 103.75, 55.51; IR (KBr)/cm^{-1} 2924, 1690, 1612, 1508, 1250, 1026, 818; HRMS (ESI): Calcd for $C_{19}H_{13}F_2N_3O_2$ ($M-H^+$) 354.1054; Found 354.1060.

6-(2-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44m)



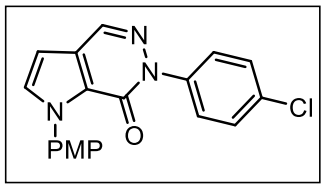
(Yellow pasty liquid, 68 mg, yield 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.49 – 7.52 (m, 1H), 7.43 – 7.46 (m, 1H), 7.41 (d, *J* = 8.9 Hz, 2H), 7.32 – 7.37(m, 3H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.65 (d, *J* = 2.9 Hz, 1H), 3.81 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.28, 153.85, 139.46, 134.56, 132.61, 132.23, 131.93, 131.36, 130.17, 129.82, 129.58, 127.53, 127.23 (2C), 125.96, 113.77 (2C), 103.74, 55.52; IR (KBr)/cm^{-1} 2924, 1612, 1512, 1504, 1296, 1250, 1026, 779; HRMS (ESI): Calcd for $C_{19}H_{14}ClN_3O_2$ (M-H$^+$) 352.0854; Found 352.0847.

6-(3-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44n)



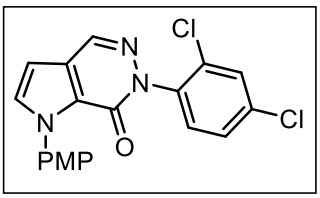
(Yellow solid, M.P =171-174 °C, 71 mg, yield 65%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.64 (t, *J* = 1.9 Hz, 1H), 7.50 – 7.53 (m, 1H), 7.39 (d, *J* = 9.0 Hz, 2H), 7.34 (d, *J* = 7.8 Hz, 1H), 7.28 – 7.31 (m, 2H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 2.9 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.48, 153.96, 142.90, 134.67, 134.04, 132.94 , 131.51, 129.38, 127.59, 127.34 (2C), 126.66, 125.69, 124.55, 123.95, 113.87 (2C), 103.54, 55.52; IR (KBr)/cm^{-1} 2924, 1674,1597, 1512, 1481, 1250, 1034; HRMS (ESI): Calcd for $C_{19}H_{14}ClN_3O_2$ (M-H$^+$) 352.0854; Found 352.0860.

6-(4-chlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44o)



(White solid, M.P =176-178 °C, 74 mg, yield 71%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.38 (d, *J* = 8.2 Hz, 4H), 7.30 (d, *J* = 3.0 Hz, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 6.62 (d, *J* = 2.9 Hz, 1H), 3.84 (s, 3H); δ 159.37, 153.98, 140.30, 134.67, 133.08, 132.93, 131.43, 128.59 (2C), 127.58 (2C), 127.34 (2C), 125.68, 122.87, 113.78 (2C), 103.53, 55.52; IR (KBr)/cm^{-1} 2924, 1728, 1659, 1520, 1466, 1250, 1095, 825, ; HRMS (ESI): Calcd for $C_{19}H_{14}ClN_3O_2$ (M-H$^+$) 352.0854; Found 352.0855.

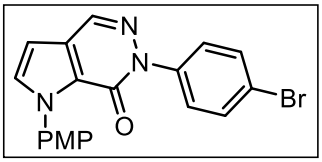
6-(2, 4-dichlorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44p)



(Brown viscous liquid, 69 mg, yield 60%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.52 (d, *J* = 1.7 Hz, 1H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.33 – 7.35 (m, 2H), 7.18 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.65 (d, *J* = 2.9 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (75 MHz,

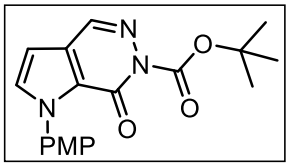
$CDCl_3$) δ 159.42, 153.80, 137.61, 134.82, 132.74, 131.31, 130.50, 130.01, 128.07, 127.76, 127.20 (2C), 126.02, 124.45, 123.96, 113.86 (2C), 103.85, 55.53; IR (KBr)/cm^{-1} 2926, 1676, 1597, 1481, 1304, 1250,1180, 1065, 972; HRMS (ESI): Calcd for $C_{19}H_{13}Cl_2N_3O_2$ ($M\text{-}H^+$) 386.0464; Found 386.0470.

6-(4-bromophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44q)



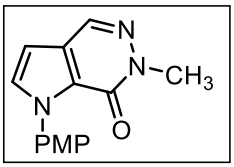
(Brown solid, M.P =186-188 °C, 82 mg, yield 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.54 (d, *J* = 9.0 Hz, 2H), 7.50 (d, *J* = 9.1 Hz, 2H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.30 (d, *J* = 2.9 Hz, 1H), 6.96 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 2.9 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.36, 153.94, 141.78, 134.74, 133.28, 132.97, 131.82, 131.56 (2C), 127.91(2C), 127.33 (2C), 125.68, 121.14, 113.78 (2C), 103.56, 55.51. IR (KBr)/cm^{-1}2924, 1666, 1582, 1520, 1466, 1296, 1250, 1011, 895; HRMS (ESI): Calcd for $C_{19}H_{14}BrN_3O_2$ ($M\text{-}H^+$) 396.0348; Found 396.0349.

***Tert*-butyl-1-(4-methoxyphenyl)-7-oxo-1*H*-pyrrolo-[2,3-*d*]pyridazine-6(7*H*)-carboxylate (44r)**



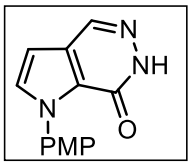
(Brown pasty liquid, 63 mg, yield 62%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.38 (d, *J* = 9.0 Hz, 2H), 7.29 (d, *J* = 3.0 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 3.0 Hz, 1H), 3.85 (s, 3H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.81, 159.35, 155.83, 135.01, 132.42, 131.39, 127.05 (2C), 121.80, 113.85 (2C), 103.73, 81.81, 55.50, 28.08, 20.52 (3C); IR (KBr)/cm^{-1} 2978, 1720, 1674, 1512, 1373, 1250, 1165; HRMS (ESI): Calcd for $C_{18}H_{19}N_3O_4$ ($M\text{-}H^+$) 342.1454 ; Found 342.1457.

1-(4-methoxyphenyl)-6-methyl-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44s)



(White solid, M.P =152-154 °C, 48 mg, yield 64%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.37 (d, *J* = 9.0 Hz, 2H), 7.23 (d, *J* = 3.0 Hz, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 6.55 (d, *J* = 3.0 Hz, 1H), 3.86 (s, 3H), 3.81 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.33, 154.39, 133.29, 132.10, 131.64, 127.31(2C), 125.88, 113.73 (2C), 103.04, 55.51, 38.83; IR (KBr)/cm^{-1} 2924, 1651, 1520, 1296, 1041, 825; HRMS (ESI): Calcd for $C_{14}H_{13}N_3O_2$ ($M\text{-}H^+$) 256.1087; Found 256.1091.

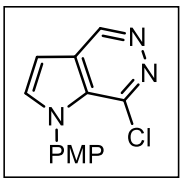
1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6*H*)-one (44t)



(Red pasty liquid, 41 mg, yield 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.39 (dd, *J* = 8.3, 6.0 Hz, 3H), 7.29 (d, *J* = 2.9 Hz, 1H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.61 (d, *J* = 2.9 Hz, 1H), 3.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.36, 135.04, 132.42, 131.34, 127.04 (2C), 126.56, 121.84, 114.09, 113.99 (2C), 103.78, 55.52; IR (KBr)/cm^{-1} 2928, 1668, 1520, 1335, 1242, 1034, 926; HRMS (ESI): Calcd for $C_{13}H_{11}N_3O_2$ (M-H$^+$) 242.0829; Found 242.0834.

5.8 Synthetic procedure for 7-chloro-1-(4-methoxyphenyl)-1*H*-pyrrolo--[2, 3-*d*] pyridazine (47)

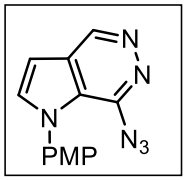
A solution of 1-(4-methoxyphenyl)-1H-pyrrolo [3, 2-*d*] pyridazin-7(6H)-one **44t** (50 mg, 0.20 mmol, 1.0 equiv.), phosphoryl chloride ($POCl_3$) (1.0 mL) and DMF (1.0 mL) was heated under reflux at 80 ºC for 1 hour. After cooling the mixture was poured under stirring onto ice/water (3.0 mL) and stirred further until solid precipitate settle down at the bottom.



(Yellow solid, M.P =162-164 °C,40 mg, yield 75%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.38 (s, 1H), 7.40 (d, *J* = 3.1 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 3.1 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.29, 145.73, 141.21, 135.01, 130.34, 129.59, 129.02 (2C), 127.17, 114.00 (2C), 102.11, 55.62; IR (KBr)/cm^{-1} 2924, 1643, 1512, 1250, 1211, 1018; HRMS (ESI): Calcd for $C_{13}H_{10}N_3O$ (M-H$^+$) 260.0590; Found 260.0585.

5.9 Experimental procedure for the synthesis of 7-azido-1-(4-methoxyphenyl)-1*H*-pyrrolo-[2, 3-*d*] pyridazine (48)

A suspension of the compound **47** (50 mg, 0.18 mmol, 1.0 equiv.), and sodium azide (18 mg, 0.28 mmol, 1.5 equiv.) in DMF (2.0 mL) was stirred at room temperature for 4 hours. The crude material was taken in saturated $NaHCO_3$ solution and extracted with ethyl acetate (2 x5 mL), the combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated under vaccum. The desired compound **48** was obtained as brown pasty liquid with 70% yield after simple chromatographic purification using EtOAc/hexane.

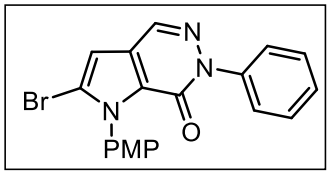


(Brown pasty liquid, 36 mg, yield 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.39 (d, *J* = 8.9 Hz, 2H), 7.37 (s, 1H), 7.28 (d, *J* = 2.9 Hz, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 2.9 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$)

δ 159.32, 134.96, 132.29, 127.02 (2C), 126.43, 124.44, 121.84, 114.09, 113.87 (2C), 103.80, 55.53; IR (KBr)/cm^{-1} 2965, 2052, 1612, 1512, 1466, 1319, 1134, 1034, 964;HRMS (ESI): Calcd for $C_{13}H_{10}N_3O$ ($M\text{-}H^+$) 267.0994; Found 267.0990.

5.10 General procedure for the synthesis of 2-bromo-1-(4-methoxyphenyl)-6-phenyl-1*H*-pyrrolo-[2, 3-*d*] pyridazin-7(6H)-one (49)

N- Bromosuccinimide (NBS) (28 mg, 0.15 mmol, 1.0 equiv.) was added to the stirred solution of 1-(4-methoxyphenyl)-6-phenyl-1H-pyrrolo [3, 2-*d*] pyridazin-7(6H)-one (**44a**) (50 mg, 0.15 mmol, 1.0 equiv.) in CH_3CN (2.0 mL) at rt and further heated at 80 ºC for 4 hrs. The reaction was cooled to room temperature and solvent were evaporated under reduced pressure. The crude material was taken in saturated $NaHCO_3$ solution and extracted with ethyl acetate (2 x5 mL), the combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated under vacuum. The corresponding bromo compound **(49)** was obtained as brown solid with 72% yield after simple chromatographic purification using EtOAc/hexane as an eluent.



(Brown solid,44 mg, yield 70%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 7.49 – 7.52 (m, 2H), 7.41 (dt, *J* = 3.9, 1.2 Hz, 2H), 7.38 (dd, *J* = 4.1, 1.9 Hz, 1H), 7.33 – 7.36 (m, 1H), 7.31 – 7.33 (m, 1H), 7.24 (s, 1H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.20,152.29, 141.39, 131.84, 129.49, 129.15 (2C), 128.60 (2C), 127.84, 127.32, 126.16 (2C), 124.12, 120.17, 113.97 (2C), 94.40, 55.45; HRMS (ESI): Calcd for $C_{19}H_{14}Br\ N_3O_2$ ($M\text{-}H^+$) 396.2643; Found 396.2648.

Notably organocatalytic direct Mannich reaction/annulations product (**49**) efficiently proceeded with mild oxidant IBX in one-pot operation. The compound (**49**) was characterized by its NMR, IR, and HRMS data. All the protons and carbons were located at their respective positions in ^{1}H and ^{13}C NMR. Additionally, HRMS peak at 295.0720 for [$M\text{-}H^+$] and carbonyl group at 1672 cm^{-1} in IR spectroscopy confirmed the structure of (**49**). A representative ^{1}H and ^{13}C NMR of (**49**) is shown in (**Figure 5.2**). Further, the structure of desired product (**44a**) was characterized by NMR, IR and HRMS data. All protons and carbons were located at their respective positions in ^{1}H and ^{13}C NMR of (**44a**). Additionally, HRMS peak at 318.1248 for [$M\text{-}H^+$] and amidic carbonyl group at 1736 cm^{-1} in IR spectroscopy confirmed the structure of (**44a**). A representative ^{1}H and ^{13}C NMR of (**44a**) are shown in (**Figure 5.3**).

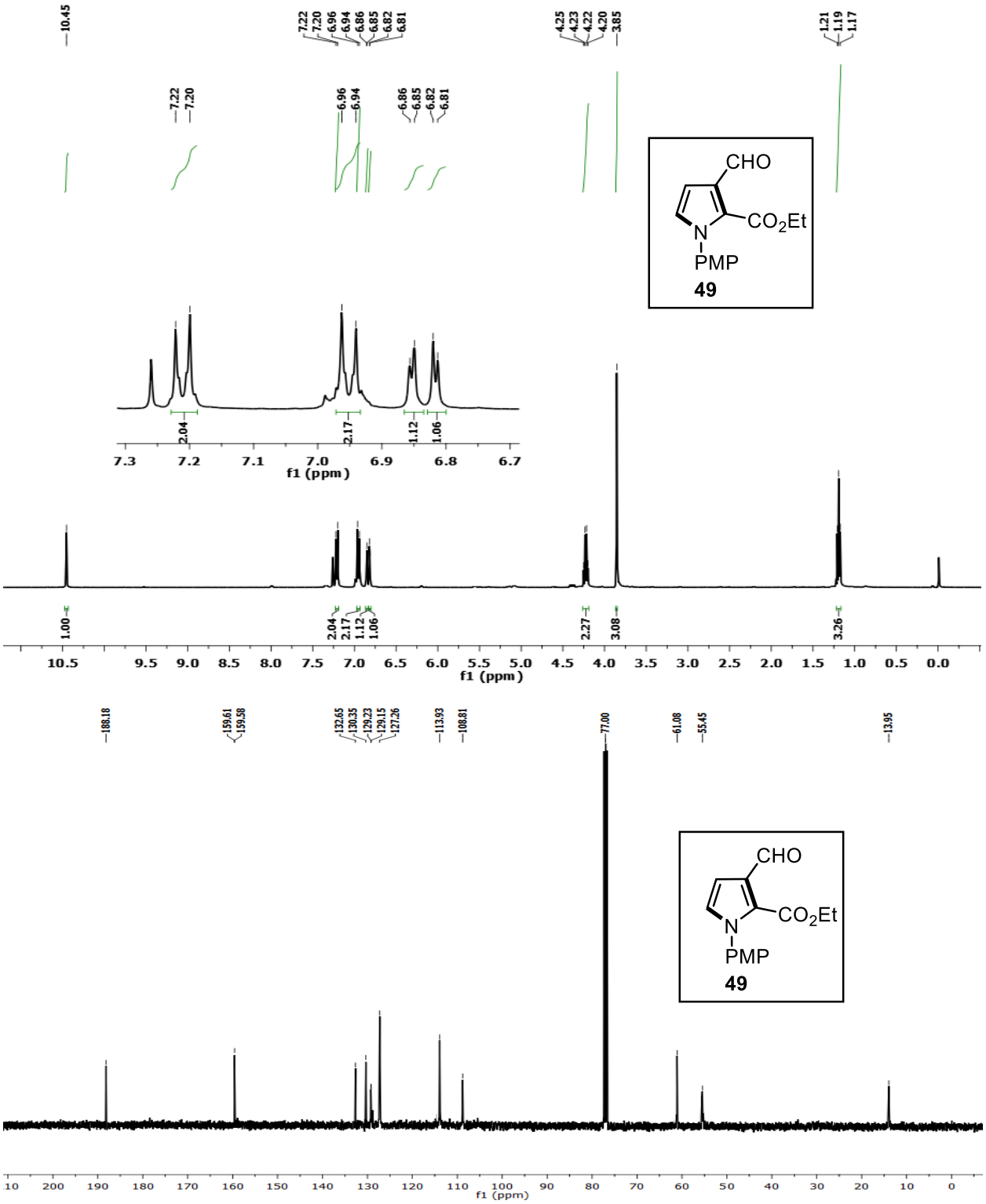


Figure 5.2 ^{1}H and ^{13}C NMR spectra of ethyl 3-formyl-1-(4-methoxyphenyl)-1H-pyrrole-2-carboxylate (**49**)

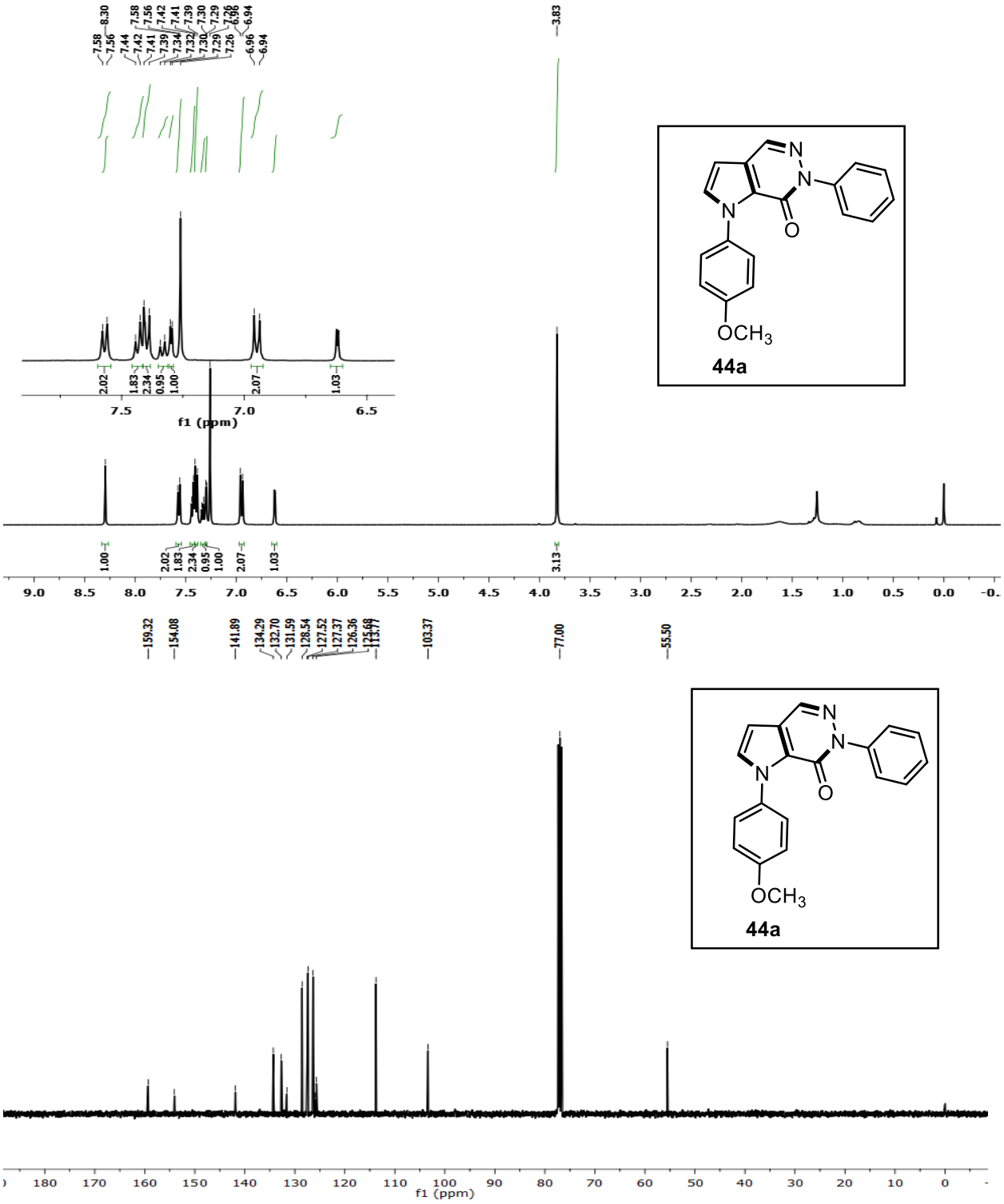


Figure 5.3 ^{1}H and ^{13}C NMR spectra of 1-(4-methoxyphenyl)-6-phenyl-1,6-dihydro-7H-pyrrolo-[2,3-*d*]pyridazin-7-one (**44a**)

4.15 Crystal structure of 6-(4-isopropylphenyl)-1-(4-methoxyphenyl)-1,6-dihydro-7*H*-pyrrolo-[2,3-*d*]pyridazin-7-one (44d) with [CCDC No. 1455374]

Table 5.3 Crystal data for **44d**

Crystal description	rod
Crystal colour	brown
Crystal size	0.3 x 0.1 x 0.1 mm
Empirical formula	C_{22} H_{21} N_3 O_2
Formula weight	359.42
Radiation, Wavelength	Mo *K*α, 0.71073 Å
Unit cell dimensions	a= 7.1067(8), b= 9.6899(10), c= 14.5223(12)Å, α = 84.346 (8), β= 77.804(8), γ =73.771(10)º
Crystal system	Triclinic
Space group	P-1
Unit cell volume	937.70(16)
No. of molecules per unit cell, Z	2
Temperature	293(2)
Absorption coefficient	0.083 mm^{-1}
F(000)	380
Scan mode	ω scan
θ range for entire data collection	3.54<θ<26.00 º
Range of indices	h= -8 to 8, k= -11 to11, l= -16 to 17
Reflections collected / unique	6364 / 3685
Absorption correction	Multi-scan Crys Alis RED
Reflections observed (I > 2σ(I))	1701
R_{int}	0.0422
R_{sigma}	0.1152
Structure determination	Direct methods
Refinement	Full-matrix least-squares on F^2
No. of parameters refined	248
No. of Restraints	0
Final R	0.0589
wR(F^2)	0.0964
Weight	$1/[\sigma^2(F_o^2)+(0.0257P)^2+0.0000P]$ where $P=[F_o^2 +2F_c^2] / 3$
Goodness-of-fit	0.957
$(\Delta /\sigma)_{max}$	0.001 (tors OSF)
Final residual electron density	-0.174 <Δρ< 0.206 eÅ^{-3}

The compound 6-(4-isopropylphenyl)-1-(4-methoxyphenyl)-1,6-dihydro-7*H*-pyrrolo-[2,3-*d*] pyridazin-7-one (C_{22} H_{21} N_3 O_2),crystallizes in the Triclinic space group P-1with unit cell unit-cell parameters: a= 7.106(8), b= 9.6899(10), c= 14.5223(12) Å, α = 84.346 (8), β = 77.804 (8)

γ=73.771(10)º and Z= 2. The crystal structure was solved by direct methods using single-crystal X-ray diffraction data and refined to R = 0.0589 for 1701 observed reflections. The crystal packing is dominated by C-H…O hydrogen bonds which link the molecules into three dimensional network. X-ray intensity data of 6364 reflections (of which 3685 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 0.30 x 0.20 x 0.10 mm. The cell dimensions were determined by least-squares fit of angular settings of 1401 reflections in the θ range 3.81 to 25.84 º**.** The intensities were measured by ω scan mode for θ ranges 3.54 to 26.00 º. 1701 reflections were treated as observed (I > 2σ(I)). Data were corrected for absorption, Extinction and Lorentz -polarisation 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. 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 = 0.0589 and wR (F^2) = 0.0964 for the observed data. Residual electron densities ranged from - 0.174 to 0.206 eÅ^{-3}. The crystallographic data are summarized in (**Table 5.3**). An *ORTEP* view of the molecule 6-(4-isopropylphenyl)-1-(4-methoxyphenyl)-1,6-dihydro-7*H*-pyrrole-[2,3-*d*]pyridazin-7-one(**44d**) showing the atom-labelling is shown in (**Figure 5.4**)

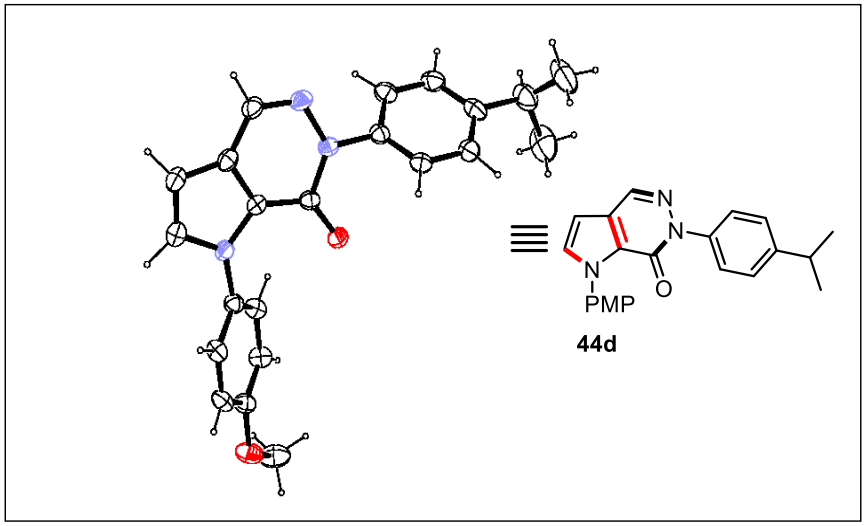


Figure 5.4 Single-crystal X-ray structure of **44d**

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Chapter VI

Conclusions

6.1 General Conclusions

In recent years, the major concern in organic synthesis is to access the potent organic complex structures in a reduced number of synthetic steps from the simple and readily available precursors. In this context, development of multistep syntheses in a single step utilizing the multi-bond forming protocols such as tandem or domino sequences, multi-component reactions and one-pot sequential reactions are given high priority in synthetic organic chemistry. Moreover, in modern synthetic field, organocatalyzed C-C, C-N, C-O, C-S, C-P and C-halide bond formation and functionalization is turned out as a most powerful tool for the construction of heterocyclic motifs and small molecule natural products (SMNPs) without the necessity of pre-activation of substrates and further environmental requirements such as vacuum lines or glove boxes. These methods offer the C-C and C-heteroatom bond formations with high efficiencies, high functional group tolerance and excellent enantio-, diastereo-, chemo- and regioselectivities. Consequently, synthesis of potent heterocyclic motifs by employing atom-economical functionalizations has become aforemost priority of the majority of synthetic chemists.

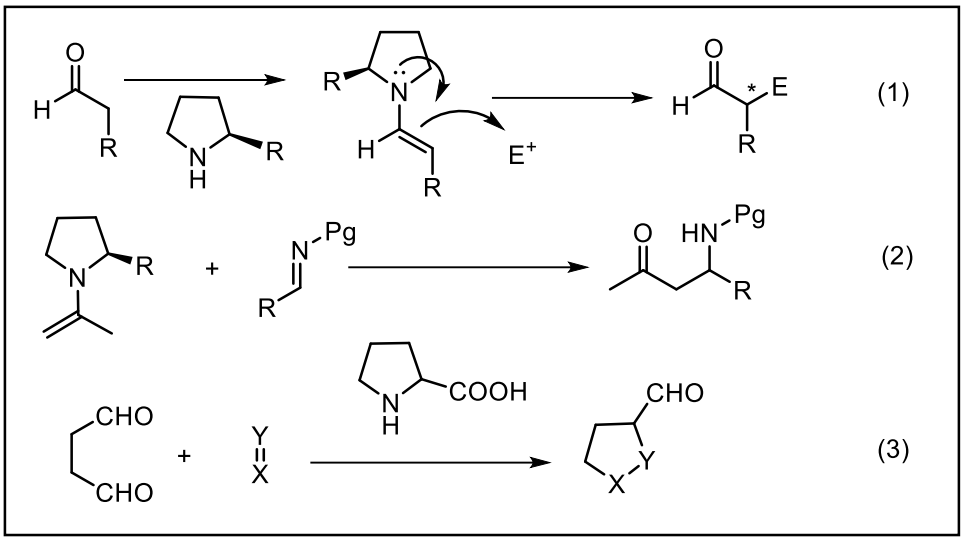
The work mentioned in this thesis entitled "**Organocatalytic approach towards the synthesis of five-membered nitrogen heterocyclic compounds**" deals with the synthesis of some selected five-membered nitrogen heterocycles such as substituted pyrrolidines, pyrroles, pyrrolo-pyridazinones in asymmetric as well as in non-asymmetric fashion. The main strategy involves [3+2] annulation between succinaldehyde or 1, 4-ketoaldehydes, with various *N*-PMP-aldimines, which involves proline catalyzed direct Mannich reaction followed by reductive or oxidative cyclization sequence. Here these dicarbonyl compounds succinaldehyde or 1, 4-ketoaldehydes acts as 1, 3-carbon *donor-acceptor* (D-A) precursors for the one-pot domino/tandem sequence with imines. The work discussed in the thesis is divided into five chapters.

6.2 Specific Conclusions

The thesis entitled "**Organocatalytic approach towards the synthesis of five-membered nitrogen heterocyclic compounds**" is divided into five chapters. A brief overview of these chapters is discussed below.

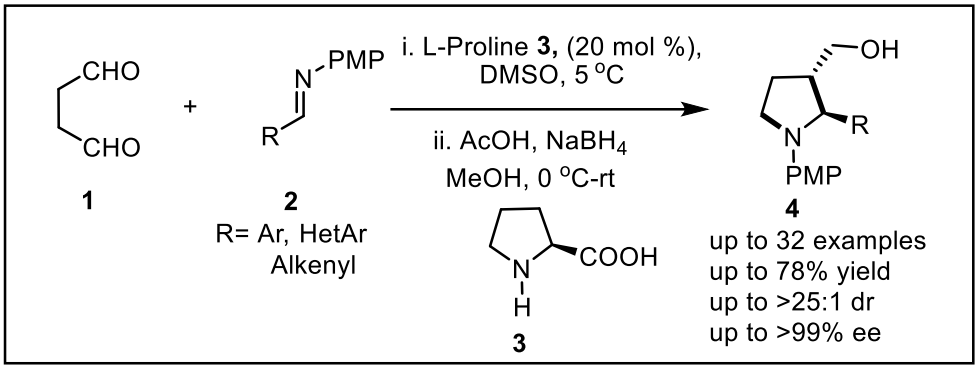
The first chapter of the thesis presents a brief discussion on organocatalysis, particularly, L-proline catalyzed direct Mannich reactions, its progress in the development of synthetic methods for complex scaffolds, synthetic drugs, and natural products. A brief description on five

membered *N*-nitrogen heterocycles and the discussion on the utilization of succinaldehyde in amino-catalytic cascade transformations are also presented (**Eqn 1, 2 and 3, Scheme 6.1**).



Scheme 6.1 Schematic representation of amine catalysis through enamine

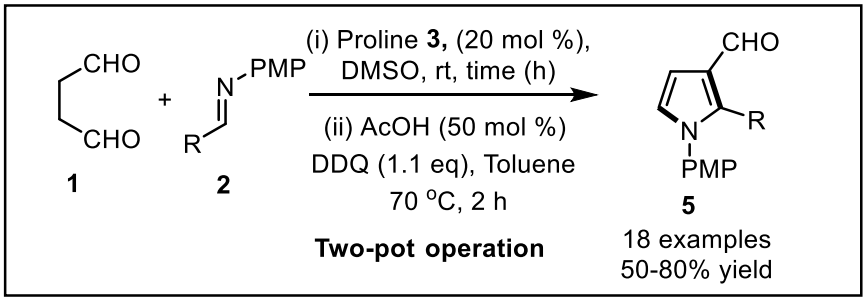
The second chapter of the thesis describes the asymmetric synthesis of *trans*-2, 3-disubstituted pyrrolidines, and related natural product based scaffolds *via* L-proline catalyzed [3+2] annulations between succinaldehyde and aldimines. This reaction proceeds through the direct Mannich reaction followed by reductive cyclization under mild conditions with high yield and enantioselectivity (**Scheme 6.2**). The synthetic application of this developed method is also shown to prepare highly functionalized and fused pyrrolidines which are present in medicinally important compounds.



Scheme 6.2 Direct Mannich-reductive [3+2] annulation for substituted pyrrolidines

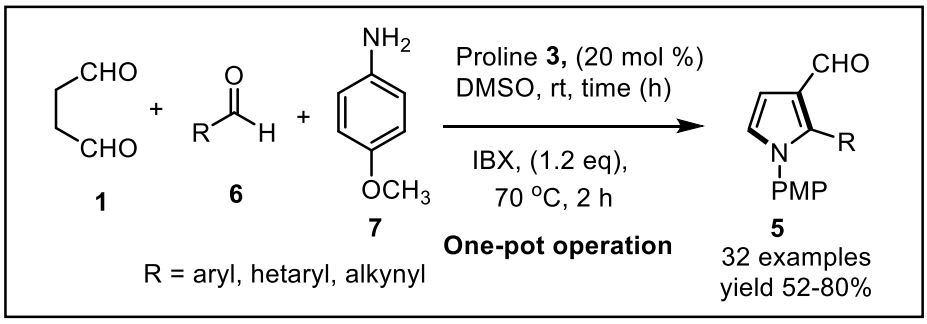
The third chapter of the thesis describes the synthesis of 2, 3-disubstituted-3-formylpyrroles by proline catalyzed direct Mannich reaction/oxidative cyclization as formal [3+2] cycloaddition process. The chapter is divided into two parts.

In part-A, a two pot strategy is described for the synthesis of 2, 3-disubstituted pyrrole-3-carboxaldehyde *via* proline catalyzed direct Mannich cyclization followed by an oxidative aromatization using DDQ as an oxidant with good yields (**Scheme 6.3**).



Scheme 6.3 Direct approaches for the synthesis of pyrrole-3-carboxaldehdye from succinaldehyde and aldimines

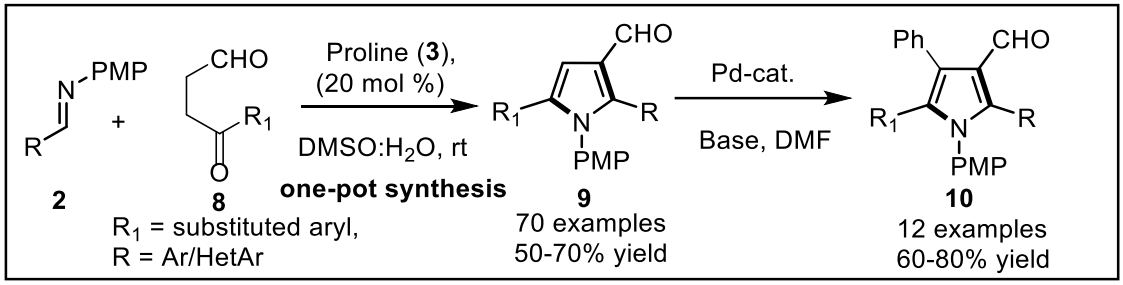
In part-B, a simple, convenient and improved one-pot procedure has been developed for the synthesis of 2, 3-disubstituted pyrrole-3-carboxaldehydes in multicomponent fashion from sucinaldehyde, aromatic aldehydes, and *p*-anisidine by using IBX as the mild oxidant (**Scheme 6.4**). The developed high yielding method has been utilized for the quick synthesis of some hybrid-heterocyclic compounds such as pyrrolo-quinolines, pyrrolo-phenanthridines, pyrrolo-oxadiazoles and pyrrolo-acrylates.



Scheme 6.4 Three-component one-pot synthesis of pyrrole-3-carboxaldehyde

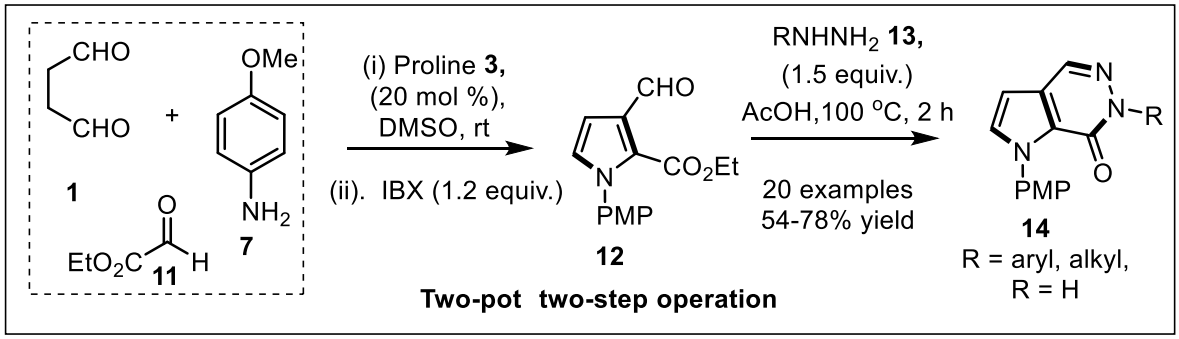
The fourth chapter of the thesis describes a highly efficient method for the one-pot synthesis of densely and fully substituted 3-formylpyrroles and related fused heterocycles under proline catalyzed conditions. Herein, direct Mannich reaction between 1, 4-ketoaldehyde and *N*-PMP

imines followed by *in situ* cyclization and aerobic aromatization takes place in same pot, thus highly substituted 3-formylpyrroles obtained in good yields (**Scheme 6.5**). The developed methodology was further applied to construct various fused heterocycles which are having tremendous applications in the field of biology and medicinal chemistry.



Scheme 6.5 Organocatalytic strategy for densely and fully substituted 3-formylpyrroles

The fifth chapter of thesis deals with the synthesis of fused pyrrolo-[2, 3-*d*]pyridazinone derivatives by employing fully organocatalytic two-pot multicomponent cascade approach using ethyl glyoxalate, *p*-anisidine, succinaldehyde and substituted hydrazines as starting material *via* direct Mannich reaction/oxidative aromatization followed by nucleophilic addition/cyclization with various hydrazines in good yields in one-pot (**Scheme 6.6**). Further applications of this developed methodology lead to the formation of azido-pyrrolo-[2, 3-*d*] pyridazines, which are having significant applications in medicinal chemistry.



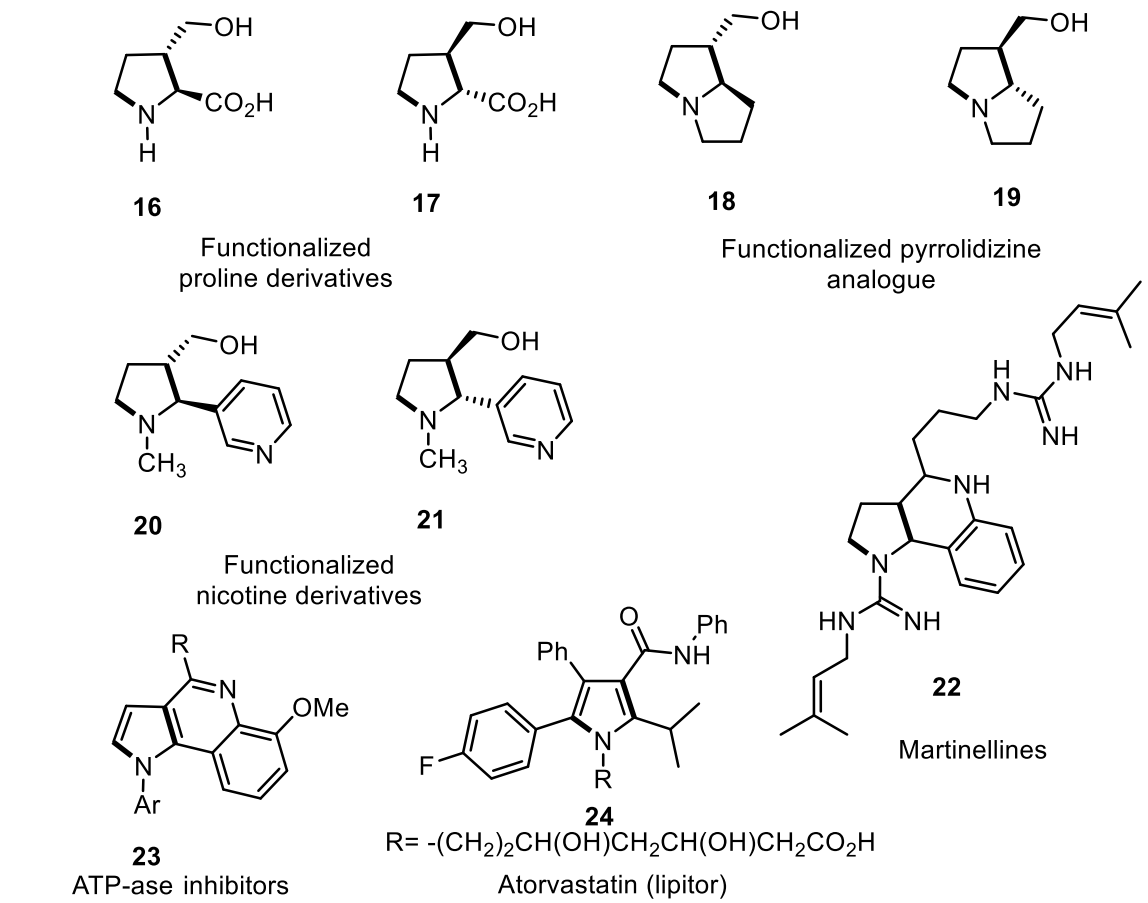
Scheme 6.6 Quick approaches to fused pyrrolo-[2, 3-*d*] pyridazinones

All the synthesized compounds presented in this thesis were identified using their spectroscopic techniques such as HPLC, IR, ^{1}HNMR, ^{13}CNMR, HRMS mass spectral data, optical rotation using polarimeter, and single X-ray diffraction. The fascinating results obtained through this study were published in different international journals. These synthetic schemes have tremendous potential for further synthesis of novel biological active compounds.

6.3 Future Scope of the Research Work

Organocatalyzed transformations deliver C-C and C-heteroatom bonds, 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. Last more than one decade has witnessed an unexpected bundle of publications with this concept and a high overflowing of synthetic libraries have been achieved using this modern activation strategy. In addition, multi-bond forming approaches like tandem reactions, multi-component reactions and one-pot sequences amalgamated with organocatalyzed activation of substrates through covalent and non-covalent interactions offer high complexity and diversity in a single step. As many natural products in addition to pharmacologically active molecules contain fused heterocyclic compounds as their central frameworks, synthesis of these molecules by means of aforementioned hybrid methodologies is a potential alternative to traditional linear syntheses.

The thesis mainly focused on the chemistry of amine catalyzed development of new methods for the synthesis of nitrogen heterocycles such as *trans*-2, 3-disubstitted pyrrolidines, substituted-3-formylpyrrole ring systems, pyrrolo-[2, 3-*d*]pyridazinones and related polycyclic heterocycles having tremendous applications in medicinal chemistry as well as in biological sciences. These *N*-fused structures have been synthesized through tandem reactions, multi-component one-pot protocols and proline catalyzed direct Mannich reaction cyclization sequence. As the synthesized molecules are the key structures of a wide range of chiral ligands, medicinally active compounds and itself used as organocatalysts. The developed procedures can be tuned further to access the drugs in a reduced number of steps or probably in a single step. These procedures have a wide scope and can be employed for the synthesis of a diverse range of either bioactive heterocyclic molecules or to access new heterocyclic libraries for biological screenings. The synthetic methodologies and novel *N*-fused heterocyclic compounds provided in the thesis will be a fine and adaptable example for the systematic construction of fused heterocycles for biological screenings. Based on our developed research methodologies, we can further utilize these ideas towards the synthesis new chiral catalysts and other biologically active scaffolds as shown in (**Scheme 6.7**) which are having tremendous applications in drug design and discovery.



Scheme 6.7 Future scope for the synthesis of pyrrolidine and pyrrole based alkaloids

Appendices

LIST OF PUBLICATIONS [A-1]

1. **Nisar. A. Mir**, Sachin Choudhary, P. Ramaraju, D. Singh, and Indresh Kumar**,** Microwave assisted aminocatalyzed [3+2] cycloaddition between α-iminonitriles and succinaldehyde: Synthesis of pyrrole-3-methylenealcohols and related polycyclic ring systems, *RSC Adv.* **2016**, *6*, 39741-39749.
2. P. Ramaraju, **Nisar. A. Mir**, D. Singh, V. K. Gupta, Rajnikant and Indresh Kumar, Enantioselective synthesis of *N*-PMP-1, 2-dihydropyridines via formal [4+2] cycloaddition between aqueous glutaraldehyde and imines, *Org. Lett.* **2015,** *17*, 5582-5585.
3. Indresh Kumar**,** P. Ramaraju, **Nisar. A. Mir,** Anoop Singh, Linear dialdehydes as promising substrates for amino catalyzed transformations, *Org. Biomol. Chem.* **2015,** *13***,** 1280-1293**.**
4. Indresh Kumar**,** **Nisar. 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, Rajnikant, Highly enantioselective [4+2] annulation *via* organocatalytic Mannich-reductive cyclization: One-pot synthesis of functionalized piperidines, *Chem. Comm.* **2013**, *49*, 564.
6. Indresh Kumar**,** P. Ramaraju, **Nisar. A. Mir**, Asymmetric trienamine catalysis: New opportunities in amine catalysis, *Org. Bio. Chem.* **2013,** *11*, 709.
7. Indresh Kumar, **Nisar. A. Mir**, Panduga R, Basant P. Wakhloo, Organocatalytic Mannich/cyclization/aromatization sequence: direct synthesis of substituted pyrrole-3-carboxaldehydes, *RSC Adv*. **2012,** *2***,** 8922-8925.
8. Indresh Kumar, **Nisar. A. Mir**, Vivek K. Gupta and Rajnikant, Organocatalytic direct Mannich/cyclization cascade as [3+2] annulations. Asymmetric synthesis of 2, 3-substituted pyrrolidines, *Chem. Commun.* **2012**, *48*, 6975-78.
9. Indresh Kumar, **Nisar. A. Mir**, C. V. Rode, B. P. Wakhloo, Intramolecular Huisgen [3+2] cycloaddition in water: Synthesis of fused pyrrolidine-triazoles, *Tetrahedron. Asymmetry.* **2012**, *23*, 225-229.
10. Kamini Kapoor, Vivek K. Gupta, Indresh Kumar, **Nisar. A. Mir,** Rajni Kant, 2-Methoxy-*N*-(4-nitrobenzyl) aniline, *Acta Crystallographica E.* **2012,** *68*, o988 (Part4)

LIST OF PRESENTATIONS [A-2]

1. Poster Presentation entitled "Organocatalytic synthesis of *N*-substituted pyrrole-[2, 3-*d*] pyridazinones from ethyl glyoxalate, *p*-anisidine, succinaldehyde and various hydrazines"during 22nd International Conference of Indian Society of Chemists and Biologists (ISCB) at Department of Chemistry, at Uka Tarsadia University, Surat, India, (**6th- 8th February 2016**).

2. Poster Presentation entitled "Synthesis of densely substituted 3-formylpyrroles from imines and 1, 4-ketoaldehydes using proline as an organocatalyst"during International Conference on "Nascent Developments in Chemical Sciences: Opportunities for Academia-Industry Collaboration" (NDCS-2015) organized by the Department of chemistry at BITS Pilani, Rajasthan, India during (**16th- 18th October 2015**).

3. Oral Presentation entitled "Organocatalytic direct Mannich/cyclization cascade towards the synthesis of densely substituted nitrogen heterocycle" during Research Scholar Day organized by department of physics, at BITS Pilani, Rajasthan (**15th March 2015**)

4. Oral Presentation entitled "Organocatalytic approach towards the synthesis of substituted pyrroles from imines and 1, 4-ketoaldehydes" during National Conference on Frontiers at the Chemistry Allied Sciences Interface (FCASI) at Department of Chemistry, University of Rajasthan, Jaipur, India (**13th - 14th March 2015**).

5. Poster Presentation entitled "Organocatalytic synthesis of densely substituted 3-formyl pyrroles from imines and 1, 4-ketoaldehydes" during 21st-International Conference of Indian Society of Chemists and Biologists (ISCB) at Department of Chemistry, CDRI, CSIR, Lucknow, U.P, India (**25th- 28th February 2015**).

6. Poster Presentation entitled "Organocatalytic direct Mannich/cyclization cascade towards the synthesis of 2, 3-disubstituted pyrrole-3-carbaldehydes." during National Conference on Nano and Functional Materials (NFM-2014) organized by department of Chemistry, at BITS Pilani, Rajasthan (**8th- 10th November 2014**).

7. Poster Presentation entitled "Organocatalytic direct Mannich/cyclization cascades towards the synthesis of 2, 3-disubstituted pyrrole-3-carbaldehydes." during International Symposium on Recent Advances in Medicinal Chemistry (ISRAM-2014) at Department of Medicinal Chemistry, NIPER, Mohali, Punjab, India (**8th- 10th September 2014**).

8. Oral Presentation entitled "Organocatalytic approach towards the synthesis of five-membered nitrogen heterocycles" during Research Scholar Day organized by department of physics, at BITS Pilani, Rajasthan (**23rd March 2014**).

9. Poster Presentation entitled "Organocatalytic asymmetric [3+2] annulations towards the synthesis of substituted pyrrolidine ring systems" during 20th International Conference of Indian Society of Chemists and Biologists (ISCB) at Department of Chemistry, University of Delhi (**1st- 4th March 2014**).

10. Oral Presentation entitled "Organocatalytic direct Mannich/cyclization cascade as [3+2] annulation: Asymmetric synthesis of 2, 3-substituted pyrrolidines" during National Conference on Recent Developments in chemical Sciences (NCRDCS) at GJUS&T, Hisar, Haryana (**25th - 26th February 2014**).

BRIEF BIOGRAPHY OF THE CANDIDATE [A-3]

Nisar Ahmad Mir obtained his master degree in Organic Chemistry from Panjab University, Chandigarh, India during 2008-10. In December 2010, he was awarded Jammu and Kashmir State Level eligibility Test (SLET) by Jammu University, Jammu for lecturership. In 2011 March, he joined Shri Mata Vaishno Devi University (SMVDU), Katra, as Research Project Fellow project entitled **"Organocatalytic asymmetric Mannich/intramolecular cyclization as formal [3+2] cycloaddition: One pot synthesis of substituted pyrrolidine ring systems"** under the kind supervision of **Dr. Indresh Kumar**, Assistant professor in Chemistry, and continued till January 2012. During this period, he involved in a variety of reactions dealing with the synthesis of diverse organic molecules such as substituted pyrrolidines and pyrrole based complex heterocyclic molecules and related carbohydrate based complex molecules. In February 2012, he was awarded Graduate Aptitude test in Engineering (GATE) in chemical sciences by MHRD, Govt. of India, New Delhi. In July 2012, he joined Department of Chemistry, BITS Pilani for PhD program under the guidance of **Dr. Indresh Kumar** with the financial assistance from the DST Sponsored Project entitled "***Organocatalysis as Green approach for synthesis of Pyrrolidine/fused Pyrrolidines: Towards the synthesis of related alkaloids***" In December 2015, he was awarded CSIR-SRF in chemical sciences by CSIR, Govt. of India, New Delhi. He has published twelve 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 fused heterocyclic motifs using covalent 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 Ph.D. 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 2014-2015 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 28 research papers 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.

RSC Advances

PAPER

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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*[,†]

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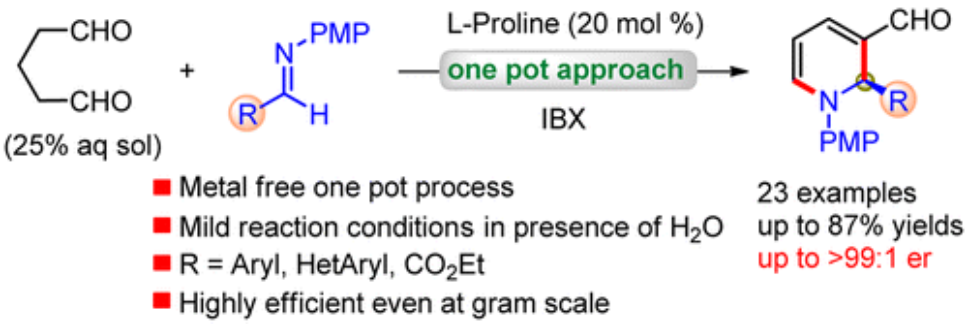

Organic & Biomolecular Chemistry

REVIEW

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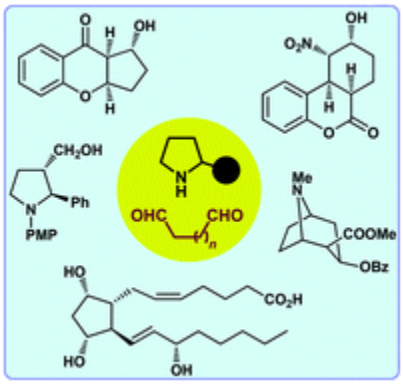
Cite this: *Org. Biomol. Chem.*, 2015, 13, 1280

Linear dialdehydes as promising substrates for aminocatalyzed transformations

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



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COMMUNICATION

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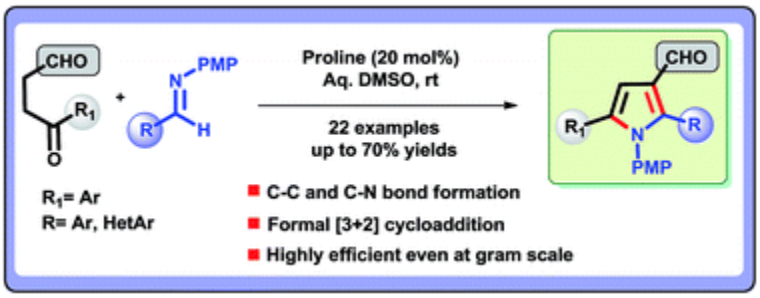
Direct catalytic synthesis of densely substituted 3-formylpyrroles from imines and 1,4-ketoaldehydes†‡

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



ChemComm

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

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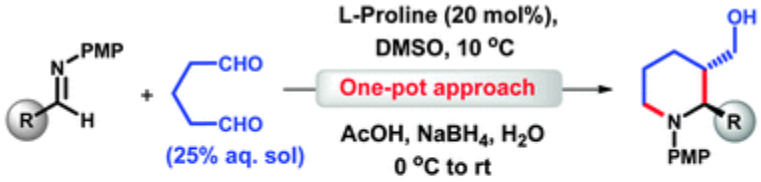
DOI: 10.1039/c3cc42431f

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

Organic & Biomolecular Chemistry

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EMERGING AREA

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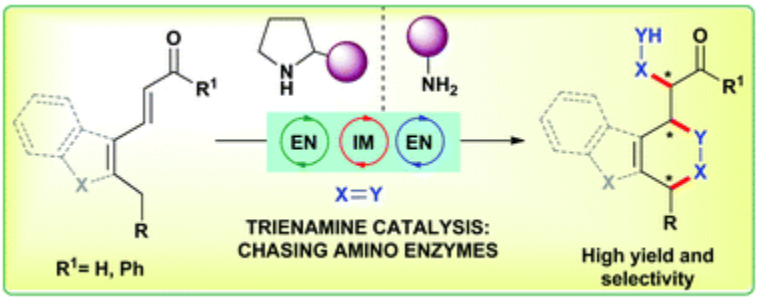
Asymmetric trienamine catalysis: new opportunities in amine catalysis†

Cite this: *Org. Biomol. Chem.*, 2013, **11**, 709

Indresh Kumar,* Panduga Ramaraju and Nisar A. Mir



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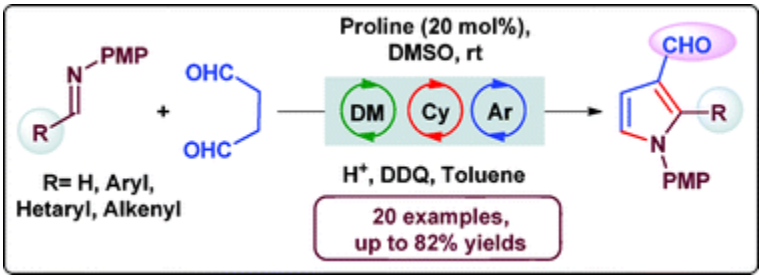
COMMUNICATION

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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COMMUNICATION

An organocatalytic direct Mannich–cyclization cascade as [3 + 2] annulation: asymmetric synthesis of 2,3-substituted pyrrolidines†

Indresh Kumar,*[ab] Nisar A. Mir,[b] Vivek K. Gupta[c] and Rajnikant[c]

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DOI: 10.1039/c2cc33103a

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Tetrahedron: *Asymmetry* 23 (2012) 225–229

Contents lists available at SciVerse ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Intramolecular Huisgen [3+2] cycloaddition in water: synthesis of fused pyrrolidine–triazoles

Indresh Kumar [a,*,†], Nisar A. Mir [a], Chandrashaker V. Rode [b], Basant P. Wakhloo [c]

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[c] Instrumentation Division, Indian Institute of Integrative Medicine (IIIM-CSIR Lab.), Canal Road, Jammu 180 001, J&K, India

organic compounds

Acta Crystallographica Section E
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4-Methoxy-*N*-(4-nitrobenzyl)aniline

Kamini Kapoor,[a] Vivek K. Gupta,[a] Indresh Kumar,[b] Nisar A. Mir[b] and Rajni Kant[a]*

[a]X-ray Crystallography Laboratory, Post-Graduate Department of Physics & Electronics, University of Jammu, Jammu Tawi 180 006, India, and [b]School of Biology & Chemistry, College of Sciences, Shri Mata Vaishno Devi University, Katra 182 320 (J&K), India
Correspondence e-mail: rkvk.paper11@gmail.com

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Data collection

Oxford Diffraction Xcalibur Sapphire3 diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2010)
T_{min} = 0.955, T_{max} = 1.000
11435 measured reflections
2511 independent reflections
1692 reflections with $I > 2\sigma(I)$
R_{int} = 0.035

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.048
$wR(F^2)$ = 0.130
S = 1.05
2511 reflections
178 parameters
H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.15 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °).

*Cg*1 and *Cg*2 are the centroids of the nitrophenyl (C1–C6) and methoxyphenyl