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Pyrrolidines: Priveleged Structure in Bioactive Molecules and Synthesis

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Abstract: ***Pyrrolidines constitute an important structural motif in natural and designed biologically active molecules. In addition, these heterocycles can be used for pharmaceutical purposesand ligands of transition metal catalysts.Pyrrolidines are also used as an effective chiral controller in various organic asymmetric transformations and are also being utilized in the synthesis of unnatural oligomers as scaffolds for various biological applications such as antidiabetic, anticancer, antimalarial, antiviral, antimicrobial, anti-inflammatory and antibacterial activities. Consequently, the efficient synthesis of these heterocycles has been received significant attention and different strategies for their syntheses have been developed. Among all the methods for the synthesis, the [3+2] cycloaddition of azomethineylides with substituted olefins is a most powerful method to rapidly obtain highly substituted pyrrolidine rings. It is intended to present a brief description of the methods for the synthesis and biological activities of pyrrolidine derivatives.***

Keywords: ***Azomethine ylides, [3+2] Cycloaddition, Pyrrolidines, Antidiabetic, Anticancer, Antimalarial, Antiviral, Antimicrobial, Anti-inflammatory, Antibacterial and antifungal activities***

I. INTRODUCTION

Pyrrolidine is a heterocyclic compounds with five membered ring have occupied an important place in bioorganic chemistry due to wide range of biological activities.[1] Among these compounds, the pyrrolidines are the most ubiquitous heterocyclic motifs found in myriad of biologically active natural products,[2] pharmaceuticals[3] and organocatalysts[4] (Figure 1). They have also serve as useful molecular scaffolds for the exploration and development of pharmacophore space *via* diversity-oriented synthesis (DOS),[5-7] culminating into new drug leads for several diseases.

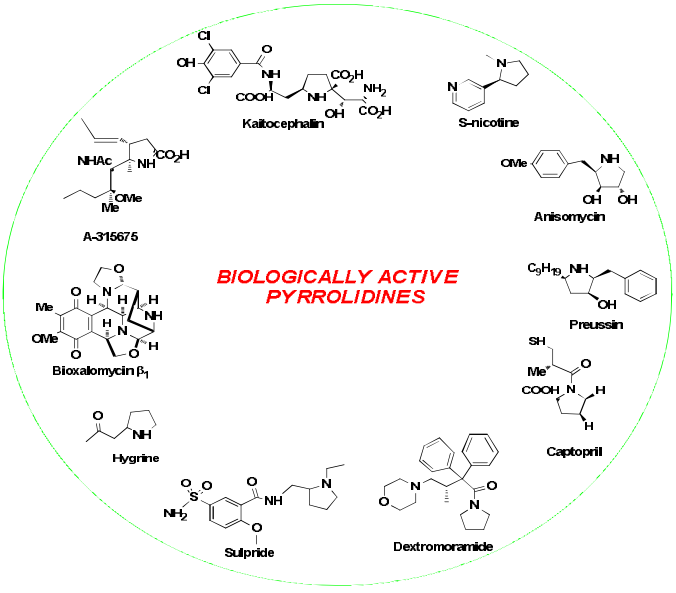


Figure 1. biologically active synthetic and natural product containing pyrrolidine unit

A. Discovery of biological activities in Pyrrolidine

The most common and simple pyrrolidine alkaloid, nicotine, isolated from the tobacco plant in 1828 by German chemists Posselt and Reimann[8a] has shown stimulant properties in mammals by activating nicotinic acetylcholine receptors (nAChRs), a family of ligand-gated ion channels widely distributed in the human brain.[8b-e] Because of their therapeutic potential for the central nervous system (CNS) disorders such as Alzheimer's, Parkinson's, and Tourette's diseases[9] the nicotine analogs have gained significance in medicinal chemistry. Hygrine, the precursor of two pharmaceutically important compounds hyoscyamine and scopolamine, is also a simple pyrrolidine alkaloid which was first isolated by Carl Liebermann in 1889 from coca leaves. Apart from this several natural products have pyrrolidine ring as substituent or fused with other rings, for example, cocaine, allosecurinine, stemofoline, quinocarcin, coccinine etc.

Being structural core of several biologically active alkaloids[10] excitatory amino acid inhibitors[11] and ACE inhibitors[12] this structural unit plays a pivotal role in elucidating biological response. Polyhydroxypyrrolidines, termed as "azasugars", are well known for their enzyme inhibitory activities[13] and possess a large number of medicinal properties. Consequently, these polyhydroxylated pyrrolidine have evoked considerable interest owing to both their enormous therapeutic potential[14-17] and applications as catalysts in asymmetric synthesis.[18]

Earlier these compounds were extracted from plants, animals and microorganism, but only very minute quantities of these compounds were obtained. Because of the low availability of these naturally occurring products, very few studies on their biological activity and mechanism of action have been performed. Therefore, this structural unit with underexplored medicinal importance are arousing considerable interest as potential therapeutic agents and as tool to understand various biological recognition processes as well as their applications as catalysts in asymmetric synthesis.[18,19]

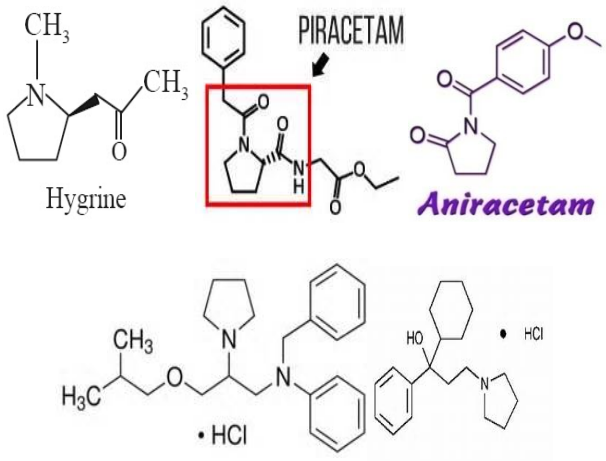
On the basis of their substitution pattern pyrrolidines can be placed under five categories: Monosubstituted pyrrolidines, disubstituted pyrrolidines, trisubstituted pyrrolidines, tetrasubstituted pyrrolidines and pentasubstituted pyrrolidines.

B. About Pyrrolidines

The pyrrolidine, also known as tetrahydropyrrole, is a five-membered cyclic amine containing four carbon atoms and one nitrogen atom and has molecular formula C4H9N. Pyrrolidines are better nucleophiles than diethylamine, principally because the lone pair is less hindered as the two alkyl substituents i.e. the ring carbons are constrained back and away from the nitrogen lone pair, and the approach by an electrophile is thus rendered easier than in diethylamine where rotations of the C-N and C-C bonds hinder approach.

C. Synthesis and occurrence

Pyrrolidine is produced by treatment of 1,4butanediol with ammonia over an oxide catalyst.[5Many modifications of pyrrolidine are found in natural and synthetic chemistry. The pyrrolidine ring structure is present in numerous natural alkaloids such as nicotine and hygrine. It is found in many drugs such as procyclidine and bepridil. It also forms the basis for the racetam compounds (e.g. piracetam, aniracetam). The amino acids proline and hydroxyproline are, in a structural sense, derivatives of pyrrolidine.



BepridilProcyclidine

D. Synthetic routes for pyrrolidines

The methods developed so far, for the synthesis of pyrrolidines involve two general categories, (a) the functionalization of the preformed pyrrolidine ring derived from a common and inexpensive material (e.g. proline),[20] and (b) construction of the pyrrolidine ring from different acyclic precursors. Intramolecular hydroamination,[21] cycloisomerization of dienes,[22] intramolecular aza-michael reaction,[23] aza-payne rearrangement,[24] double-michael reaction,[25] reductive cyclization of acetylenic aldehydes,[26] [3+2]-annulation,[27] alkenylative cyclization,[28] annulation reaction of 1,1-cyclopropanediesters,[29] *N*-heterocyclization of primary amines,[30] iodo-aldol cyclization,[31] reduction of substituted pyrroles,[32] ionic iodine atom transfer cyclization[33] and cyclization of γ-(*N*-substituted) alkenes with aryl bromide[34] are reported in the second category.Another traditional method to effect the pyrrolidine ring formation involves intramolecular cyclization of a nitrogen nucleophile onto a pendant olefin using activating reagents such as I_2 or $Hg(OAc)_2$.[2,35] The [3+2] cycloaddition[36-39] of azomethine ylides (**I**) with substituted olefins (**II**) is a most common method for rapid access of substituted pyrrolidine rings (Figure 2).

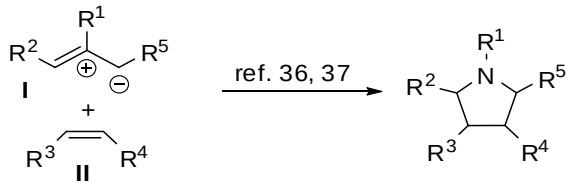
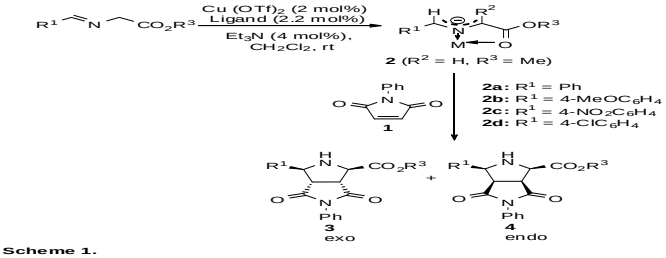


Figure 2.

A number of methods have been explored for the generation of AMY, for example, ring opening of aziridines *via* thermolysis or photolysis,[40] the 1,2 prototropy/metallo-azomethine ylides of imine derivative of amino acid,[41,42] proton abstraction from iminium salts of α-amino acids,[43,44] desilylation of various silylamino derivatives,[45-46] the decarboxylation condensation of amino acids[47] and dehydrohalogenation of iminium salts.[48]

1) *Intermolecular Cycloaddition Reactions of AMY:* In the last few years, extensive studies have been performed in the area of asymmetric [3+2]-cycloaddition of azomethine ylides employing all three possible combinations such as i) Reactions between chiral AMY and achiral dipolarophile, ii) between chiral dipolarophile and achiral AMY, iii) use of chiral catalyst. The asymmetric [3+2]-cycloaddition of azomethine ylides were most recently reviewed in 2006 by Pandey et al.[49] and its intramolecular version was covered by Coldham and Hufton in 2005.[50] Both of these reviews gave an in-depth account of asymmetric [3+2]-cycloaddition of azomethine ylides. In this review we are only incorporating recent advancement of chiral catalysts which are recently used in asymmetric [3+2]-cycloaddition of azomethine ylides.
2) *Chiral Catalyst*:In recent years, this approach has been investigated thoroughly for the synthesis of stereochemically pure pyrrolidines, however, such type of dipolar cycloaddition is still in the developmental stage.[51,52]The first example of chiral Lewis acid complex mediated stereoselective cycloadditions of the azomethine ylides was reported by Grigg and coworkers.[53] Recently, Oderaotoshi et al.[54] reported *exo*-selective cycloaddition reaction between various *N*-metalated azomethine ylides **2** and *N*-phenylphthalimides (**1**) catalyzed by $Cu(OTf)_2$ along with the chiral phosphine ligands such as (R,R) and (S,S)-CHIRAPHOS, (R,R)-DIOP, (R)-BINAP, (R)-H_8-BINAP, (R)-SEGPHOS etc. (Scheme 1)



Scheme 1.

Sansano et al.[55] have utilized the catalytic complex Ag(binap)-ClO_4 (**7**) during enantioselective 1,3-dipolar cycloaddition of an azomethine ylide, generated from imino esters **5**, and NMM **6** to give cycloadduct *endo*-**8** in 89-91% yield with >99% ee was obtained. The beauty of this cycloaddition, is the recovery of catalytic complex (**7**) in very high yield (>90%) and its good reusability without any additional purification (Scheme 2).

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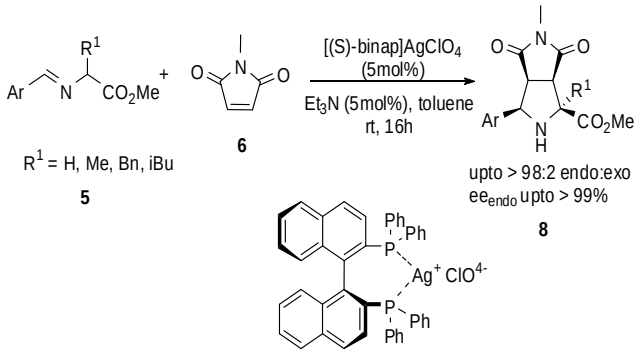
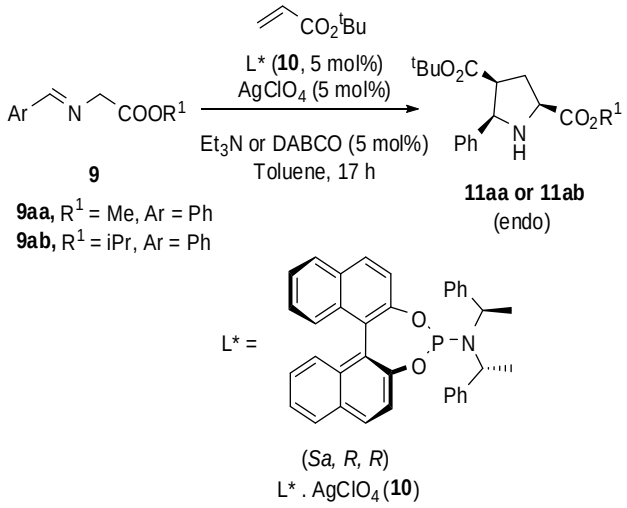


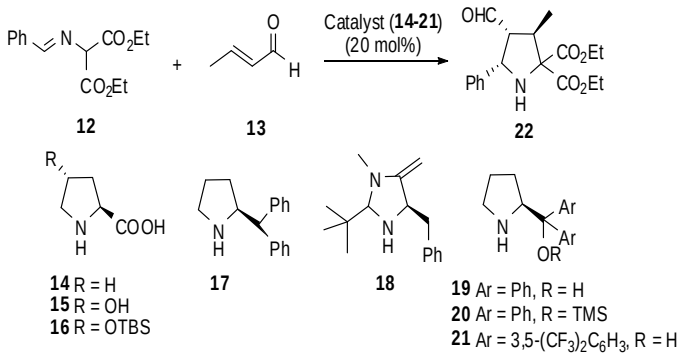
Scheme 2.

They recently reported[56] the cycloaddition of 1,3-dipoles derived from iminoglycinates **9** (**aa** or **ab**) with different dipolarophiles in the presence of novel monodentate phosphoramidite–silver complex **10** as shown in Scheme 3. In all cases the *endo* adduct (**11a-k**) was obtained as the major stereoisomer with a dr (98:2).



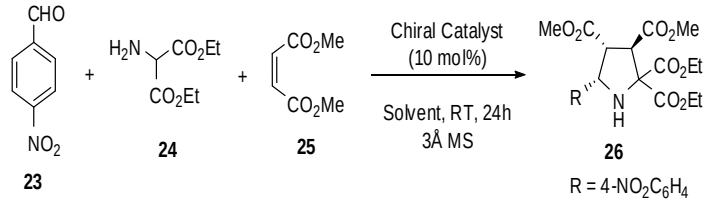
Scheme 3.

Vicario et al.[57] investigated the effect of various amine catalyst during cycloaddition of imine **12** and α, β-unsaturated aldehyde (e.g. crotonaldehyde **13**). The cyclic amino acid proline (**14**) catalyzed the reaction very efficiently to afford the single *endo* cycloadduct **22** in good yield but with only moderate enantioselectivity (ee 72%) (Scheme 4).



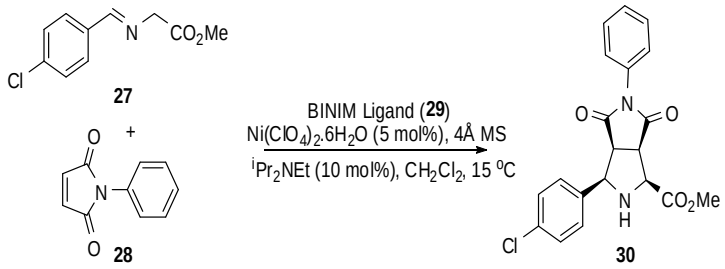
Scheme 4.

Gong et al.[58] described a Brønsted acid catalyzed three-component asymmetric cycloaddition reaction between aldehyde **23**, amino ester **24**, and dipolarophiles **25** in the presence of a chiral catalyst derived from the (*R*,*R*)-linked BINOL (Scheme 5).



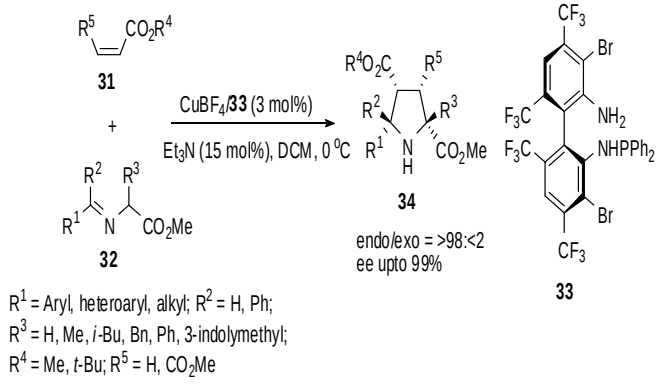
Scheme 5.

Similarly, other group[59] found chiral binaphthalenediimine (BINIM) ligand **29**, as an effective chiral ligand for Ni(II)-promoted 1,3-dipolar cycloaddition of azomethine ylides **27** and *N*-phenylmaleimide **28** to give the corresponding *endo* cycloadduct **30** in good to high yield and enantioselectivity (ee upto 82%) (Scheme 6).



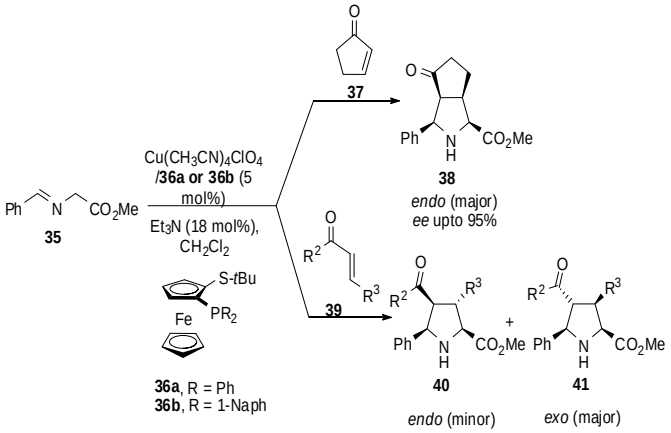
Scheme 6.

Wang et al.[60] discovered that CuI/TF-BiphamPhos complex **33** served as a novel and highly efficient catalyst for the asymmetric 1,3-dipolar cycloaddition reaction of various imino ester **32** and dipolarophile **31** to give *endo*-cycloadduct**34** as the sole product with 97% yield and upto 99% ee (Scheme 7).



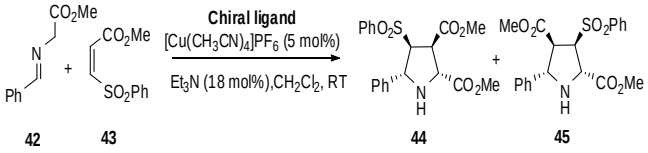
Scheme 7.

Carretero et al.[61] investigated the cycloaddition of aryl imines of glycine methyl ester **35** with cyclic enones such as cyclopentenone **37** and isolated the corresponding *endo*- bicyclic pyrrolidine **38** with high *endo*-selectivity (*endo*/*exo* = 90:10), enantioselectivity (94% ee), and chemical yield (70%), however, cycloaddition with *trans*-acyclic enones **39** took place with high *exo*-selectivity (*endo/exo* = 2:98), with an excellent enantiocontrol (upto 96% ee for the major *exo* isomer) (Scheme 8).



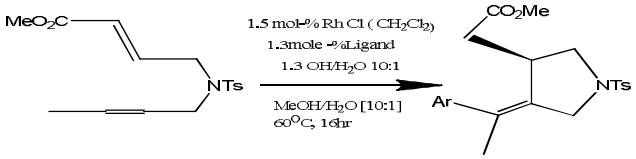
Scheme 8.

They further extended[62] this workto the Cu-catalyzed cycloaddition of methyl (*E*)-3-phenylsulfonylpropenoate (**43**) and *N*-benzylideneglycine methyl ester (**42**) in the presence of different ligands such as JOSIPHOS, TANIAPHOS, (S,S)-CHIRAPHOS, (S,S)-NORPHOS, (S)-PHANEPHOS, (R)-BINAP, (R)-SEGPHOS etc. resulting in the exclusive formation of the *exo* isomer (Scheme 9).

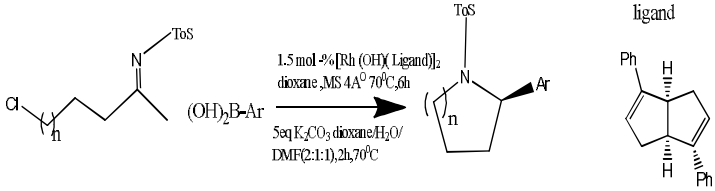


Scheme 9.

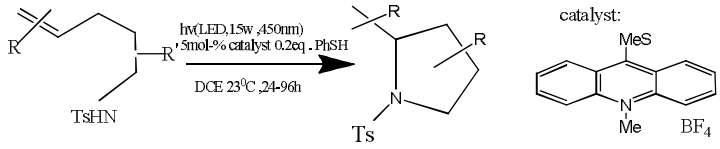
*3) Rhodium – catalysed synthesis:*A rhodium-catalyzed asymmetric arylative cyclization of nitrogen-tethered alkyne-enoate with arylboronic acids, in which two new carbon-carbon bonds and onestereocenter are formed, provides access to pyrrolidines and piperidines with good enantioselectivities by to the use of a C1-symmetric chiral monosubstituted diene ligands.
F. Serpier, B. Flamme, J.-L. Brayer, B. Folléas, S. Darses, Org. Lett., **2015**, 17, 1720-1723.



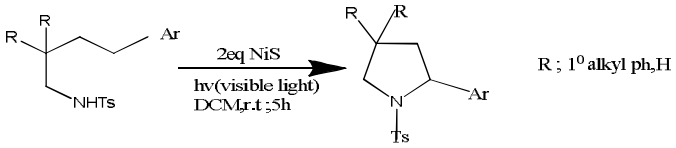
The combination of chiral bicyclo[3.3.0]octadiene ligands, an active rhodium hydroxide complex, and neutral reaction conditions en abled a
highly enantioselectiverhodium-catalyzed arylation of aliphatic N-tosylaldimines in high yield. The application of this method is de monstrated by the enantioselective synthesis of chiral 2-arylpyrrolidines and piperidines in a one-pot procedure.Z. Cui, H.-J. Yu, F.-F.Yang, W.-Y. Gao, C.-G. Feng, G.-Q. Lin, J. Am. Chem. Soc., **2011**, 133, 12394-12397



4) *Metal free method for a direct anti Markovnikov hydroamination of unsaturated amines:* A metal-free method for a direct anti-Markovnikov hydroamination of unsaturated amines is enabled by irradiation of the amine substrates with visible light in thepresence of catalytic quantities of easily synthesized 9-mesityl-10-methylacridinium tetrafluo roborate and thiophenol as a hydrogen-atom donor.The reaction furnished nitrogen-containing heterocycles with completeregiocontrol.T. M. Nguyen, D. A. Nicewicz, J. Am. Chem. Soc**., 2013**, 135, 958 8-9591.

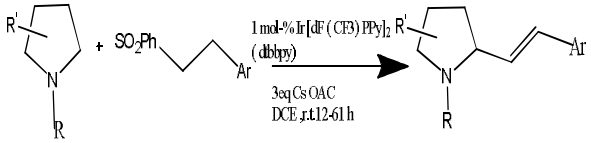


5) *Hofmann-Löffler reaction:*-Iodosuccinimide promotes an attractive and productive protocol for the position-selective intramole cular C-H amination of aliphatic groups (Hofmann-Löffler reaction)employing sulfonimides as nitrogen sources initiated by vis ible light. The overall transformation provides pyrrolidines under mild and selective conditions asdemonstrated for 17 different substrates.C. Q. O'Broin, P. Fernández, C. Martínez, Kilian Muñiz, Org. Lett**., 2016,** 18, 436-439.



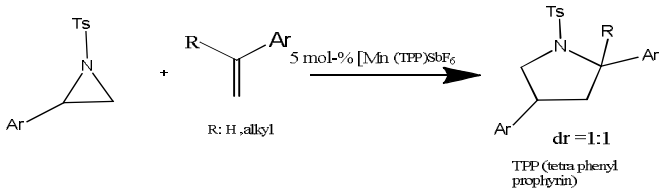
The union of vinyl sulfones with photoredox-generated α-amino radicals enables direct C-H vinylations of N-aryl tertiary amines, as well as decarboxylative vinylationsof N-Boc α-amino acids, to provide allylic amines of broad diversity in high yield and with exce llent olefin geometrycontrol. The utility of this reaction has been demonstrated via the syntheses of several natural products and a number of established pharmacophores.A. Noble, D. W. C.

MacMillan, J. Am. Chem. Soc., **2014,** 136, 11602-11605.



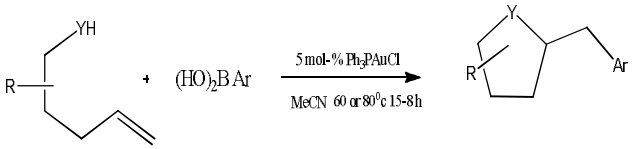
cationic manganese porphyrin catalysed synthesis

A cationic manganese porphyrin catalyst enables a formal [3+2] cycloaddition between aziridines and styrenes to give the correspon ding pyrrolidines. T. Ozawa, T. Kurahashi, S. Matsubara, Synlett, **2013**, 24, 2763-2767

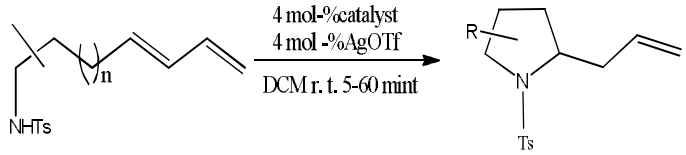


6) *via oxidative gold catalysed synthesis:*Homogeneous carboamination, carboalkoxylation and carbolactonization of terminal alkenes are realized via oxidativ e gold catalysis, providing expedient access to various substituted N- or O-heterocycles. Deuterium-labeling studies established the nature of the alkene functionalization and t

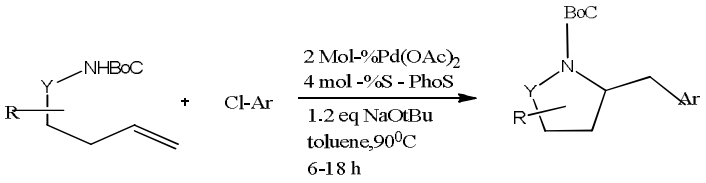
he indispensible role of Au(I)/Au(III)catalysis.G. Zhang, L. Cui, Y. Wang, L. Zhang, J. Am. Chem. Soc., **2010**, 132, 1474-147



*7) By silver triflate efficiently catalyzes a cycloisomerization of 1,3-dienes :*The combination of carbaboranylmercuric chloride as a bulky Lewis acid and silver triflate efficiently catalyzes a cycloisomerization of 1,3-dienes at room temperatureto give allyl-su bstituted azacycles and cycloalkanes in excellent yields with very high regioselectivity.H. Yamamoto, I. Sasaki, S. Shiomi, N. Yamasaki, H. Imagawa, Org. Lett**., 2012, 14**, 2250-2253

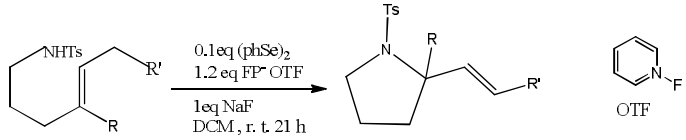


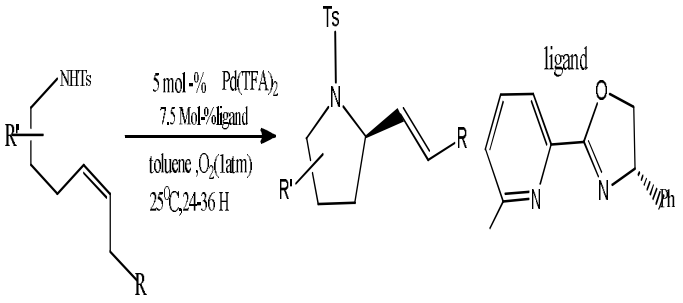
A catalyst composed of Pd(OAc)2 and S-Phos allows the conversion of aryl chlorides as electrophiles in Pd-catalyzed alkene ca rboamination and carboetherification,minimizes N-arylation, and prevents formation of regiosisomieric mixtures. Various heter ocycles, including pyrrolidines, isoxazolidines, tetrahydrofurans, andpyrazolidines, are efficiently generated with this method.B . R. Rosen, J. E. Ney, J. P. Wolfe, J. Org. Chem., **2010**, 75, 2756-275



8) Organoselenium catalysed synthesis:

Organoselenium catalysis enables an efficient synthesis of oxygen and nitrogen heterocycles via exo-cyclization under mild con ditions in the presence of 1fluoropyridinium triflate. The reaction offers good functional group tolerance and excellent regiosele ctivity.R. Guo, J. Huang, H. Huang, X. Zhao, Org. Lett., **2016**, 18, 504-507.

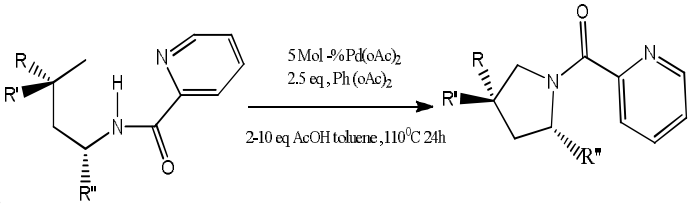




B. Weinstein, C. P. Tam, S. S. Stahl, Org. Lett., **2011, 13**, 2830-2833

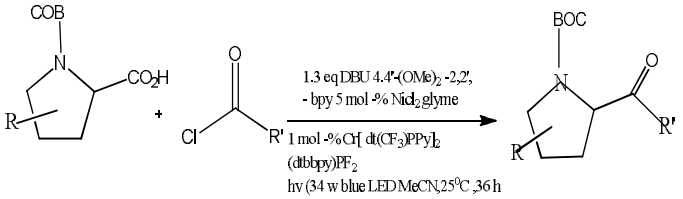
Palladium-catalyzed intramolecular amination of unactivated C-H bonds at the γ and δ positions of picolinamide (PA) protected ami ne substrates enables thesynthesis of azetidine, pyrrolidine, and indoline compounds. The method features relatively low catalyst loa

ding, use of inexpensive reagents,convenint operatingconditions and predictable selectivities.G. He, Y. Zhao, S. Zhang, C. Lu, G. C

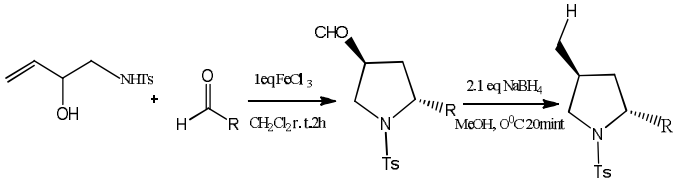


hen,J. Am. Chem. Soc., **2012**, 134, 3-6.

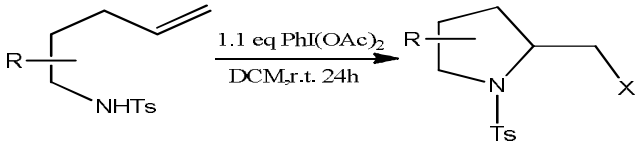
9) Metallaphotoredox catalysed synthesis:A wide variety of mixed anhydrides formed in situ from carboxylic acids and acyl chlorides can subsequently underg o metal insertion-decarboxylation-recombination to provide ketones in very good yield when subjected to metallaphotoredox catalysis. A three-step synthesis of the medicinal agent edivoxetine is also described.C. Le, D. W. C. MacMillan, J. Am. Chem. Soc., **2015**, 137, 11938-11941



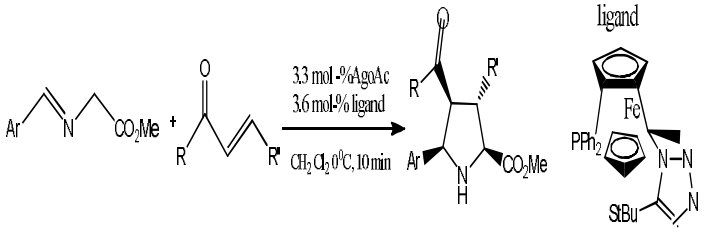
10) Alkene aza-Cope-Mannich cyclization between 2-hydroxy homoallyl tosylamine and aldehydes in the presence of iron(III) salts: An efficient alkene aza-Cope-Mannich cyclization between 2-hydroxy homoallyl tosylamine and aldehydes in the presence of ir on(III) salts gives 3-alkyl-1- tosyl pyrrolidines in good yields via a γ-unsaturated iminium ion, 2-azonia-[3,3]-sigmatropic rearrangement, and intramolecular Mannich reaction. The cyclization of 2hydroxy homopropargyl tosylamines gives dihydro-1H-pyrroles.R. M. Carballo, M. Puri no, M. A. Ramírez, V. S. Martín, J. I. Padrón, Org. Lett**., 2010, 12**, 5334-5337



In the presence of 1.1 equiv of (Diacetoxyiodo)benzene (PIDA) and suitable halogen sources, a variety of olefins underwent haloam idation, haloetherification, and halolactonization to the corresponding 1,2-bifunctional cyclic skeleton in very good isolated yields. Subsequent mild nucleophilic substitution gives key intermediatesfor biologically interesting compounds in high yields.G.-Q. Liu, Y.-M. Li, J. Org. Chem., **2014**, 79, 10094-10109.



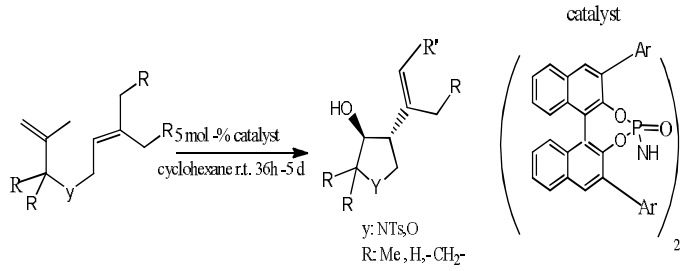
*11) 1,3-Dipolar Cycloaddition of Azomethine Ylide with α-EnoneCatalyzed by a Silver(I)/ThioClickFerrophos :*Highly Endo-Selecti ve and Enantioselective 1,3-Dipolar Cycloaddition of Azomethine Ylide with α-Enones Catalyzed by a Silver(I)/ThioClickFerr ophos ComplexI. Oura, K. Shimizu, K. Ogata, S.-i. Fukuzawa, Org. Lett., **2010**, 12, 1752-1755.



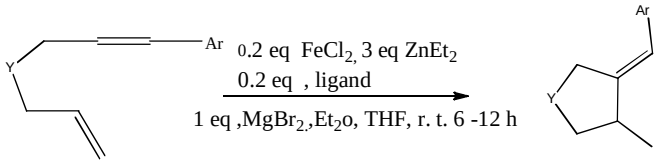
12) imidodiphosphate catalysed synthesi:

Using a confined imidodiphosphate catalyst, a highly enantioselective intramolecular carbonyl-ene reaction of olefinic aldehyde s delivers diverse trans-3,4disubstituted carbo- and heterocyclic five-membered rings in high yields and with good to excellent diastereo- and enantioselectivities.

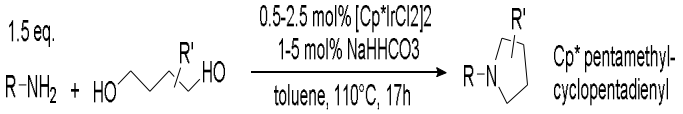
L. Liu, M. Leutzsch, Y. Zheng, M. W. Alachraf, W. Thiel, B. List, J. Am. Chem. Soc., **2015**, 137, 13268-13271.



FeCl2 and an iminopyridine ligand form in the presence of diethylzinc and magnesium bromide etherate an active catalyst for the re ductive cyclization of 1,6-enynes togive pyrrolidine and tetrahydrofuran derivatives from N- and O-tethered 1,6-enynes.A. Lin, Z.-W. Zhang, J. Yang, Org. LettA rhodium-catalyzed ., **2014, 16**, 386-389.

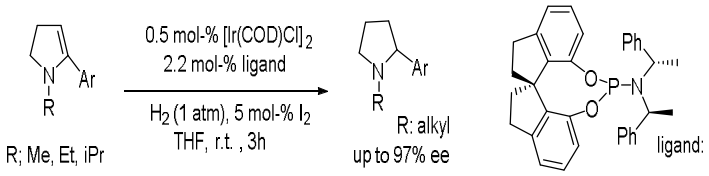


*13) Irirdium catalysed synthesis:*Fujita et al.[1] have reported Cp*Ir complex catalysed N-heterocyclisation of primary amines with alkane diols resulting into five membered cyclic amines in good to excellent yeilds.

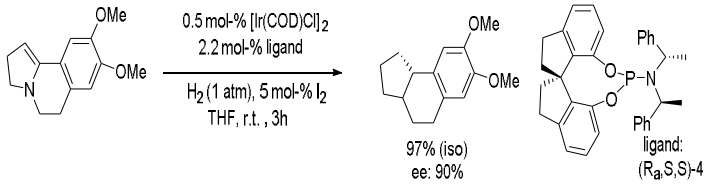


Green aspect of reaction is that method involves one step process with easy available starting material and without generating harmful products (H_2O only as by product).

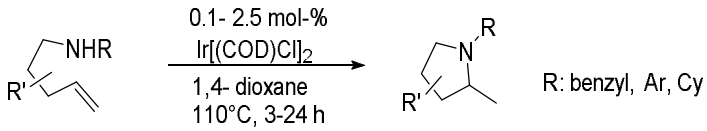
Hau et al.[2] synthesized cyclic tertiary amines in high enantioselective ratio via iridium catalyzed hydrogenation of cyclic enamines.



synthesis of natural product cryspine A.

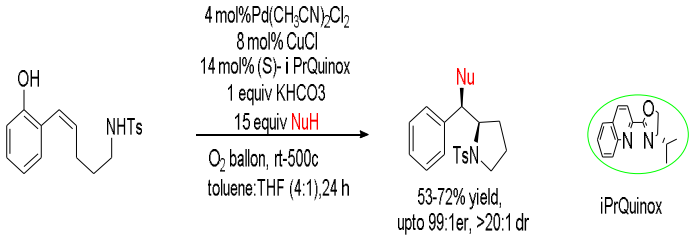


$[Ir(COD)Cl]_2$ in absence of any ligands and cocatalyst act as effective precatalyst in intramolecular hydroamination of unactivated alkene with pendant secondary alkyl or aryl amine.[3] low catalyst loading without need of added ligands and co-catalyst make $[Ir(COD)Cl]_2$ a commercially available late metal catalyst system.[4]

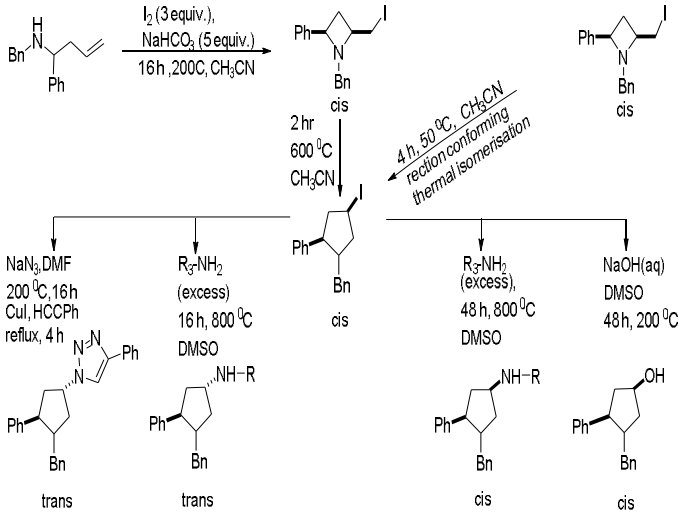


(1). Fujita, K.I.; Fujii, T.; Yamaguchi, R. Org. Lett., 2004, 6, 3525-3528. (2). Hou, G.H.; Xie, J.H.; Yan, P.C.;. Zhou, Q.L. J. Am. Chem. Soc., 2009, 131, 13661367. (3) Hesp, K. D.; Stradiotto, M. Org. Lett., 2009, 11, 14491452.(4) Liu, Z.; Hartwig, J. F. J. Am. Chem. Soc. 2008, 130, 1570.

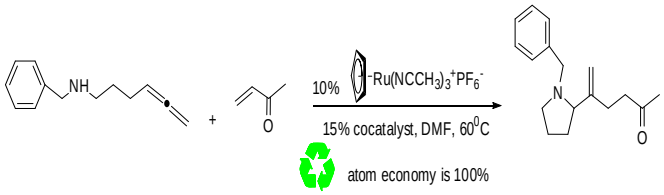
14) Palladium catalyzed synthesis of substituted pyrrolidine :Specific alkenes namely ortho-vinyl phenols undergoes difunctionalization reaction whose first step involves intramolecular nucleopalladation of tethered amines leading to Pd(II)-alkyl interm ediate containing pyrrolidine moiety which subsequently undergoes redox reaction to form ortho quinone methide intermediate. Lastly an exogenous nucleophile gets trapped intermolecularly to afford high enantio and diastereoselective products.



15) *Synthesis of Iodine catalyzed stereoselective pyrrolidine*:2,4-cis pyrrolidine derivatives can effectively be syntheised in a one pot reaction from homoallylamines which stereoselectively delivers funtionalised cis 2-(iodomethyl) azetdine as a cyclised intermediate at room temperature in excellent yield of 96%, prone to give corresponding isomerised cis-2,4-pyrrolidine at mild heating confirmed by separate heating of azitedine at 50^0C in acetonitrile for 4 hours .trans pyrr-olidine are generated by nucleophilicly replacing iodine, however adjusting addition sequence & temperature by stirring cis-azetidines with primary amines in DMSO at room temperature respectively would give cis-diastereoisomer with excellent of yield of above 77%.



16) *Ruthenium catalysed synthesis:*Trost et, Al.,[2]extended his success of ruthenium catalyse cycloetherification in an analogous way to synt-hesise pyrrolidine using secondary amines as a nucleophile ,1.5 eqiv of MVK(methyl vinyl ketone) , 10mol% of ruthenium complex as catalyst ,15 mol% of titanium chloride as cocatalyst,in DMF at 60^0C.



Effect w.r.t strength of lewis acid acting as cocatalyst is given below

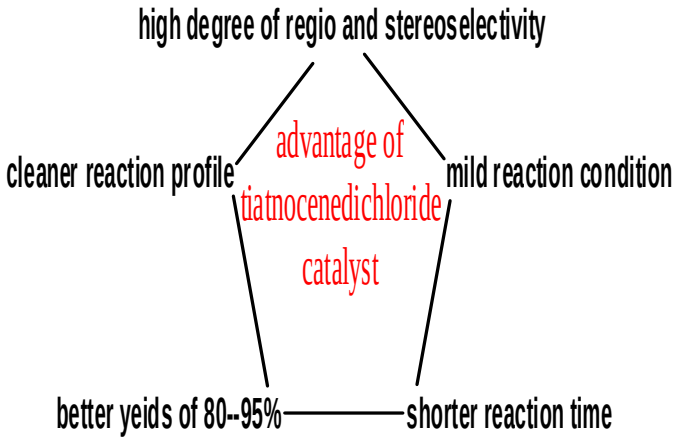
Entry	Cocatalyst	Isolated Yield%
1	$CeCl_3.7H_2O$	21
2[a]	$CeCl_3.7H_2O$	42
3[a]	$SnCl_4.5H_2O$	59
4[a]	CH_3AlCl_2	69
5[a]	$TiCl_4$	73
6[a]	None	0
7[a,b]	$TiCl_4$	0

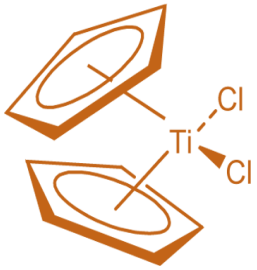
[a] Reaction worked up with pyrrolidine, [b] Run with no catalyst.

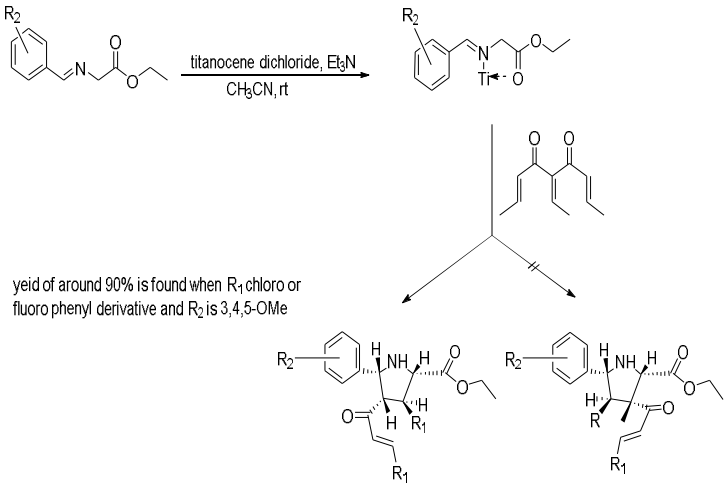
17) *20 Synthesis through 1,3-dipolar cycloaddition reaction:*Huisgen and co-worker[1] investigated the major portion of work on classic combination reaction between dipolar species (1,3-dipole) and an dipolarophile (unsaturated acceptor) leading to neutral five memebered heterocycles. Catalytic asymmetric synthesis of enantioselective proline derivative through1,3-dipolar cycloaddittion is a straight forward atom economical method.[2]

a) 1,3-dipolar cycloaddtion reaction using N-metallated azomethine ylide as a dipolar species:

i) Titanium metal catalyzed reaction: Ramaligan et. al.,[3] reported a two step, regeoselective , facile synthesis of pyrrolidine involving cycloaddtion of N-metallated azomethine ylide with tryarylideneacetyacetone using titanocenedichloride as a catalyst and triethylamine as solvent.

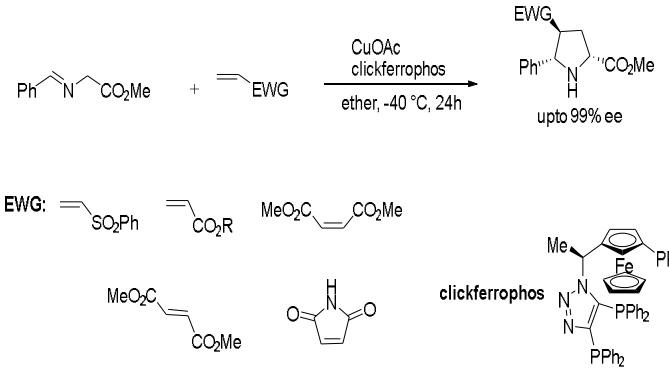






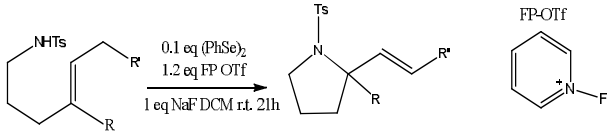
Huisgen, R.Angrew. chem. Int. Ed. Engl. 1963, 2, 565,633 (2). Stanley, L. M.; Sibi, M. P. Chem. Rev. 2008, 108, 2887–2902.(3) Murugan, R.; Raghunathan, R.; Narayanan, S.S. Synth. Comm. 2009. 39. 1936-1948.

b)1 .Copper metal catalyzed 1,3-dipolar reaction using azomethine ylide as dipolar species: Fukuzawa et al.,[1] reported facile asymmetric 1,3-dipolar reaction of azomethine ylide (N-benzylideneglycinate) with vinyl sulfone, acrylate, maleate,fumarate and maleimide (dipolarophiles) to obtain 2,3,4- and 2,3,4,5-substituted exo pyrrolidine derivative with high diastereo- and enantioselectivity catalaysed by copper(I)/clickferrophos which is 1,5-diphosphine resembling structural similarity with taniaphos.[2]



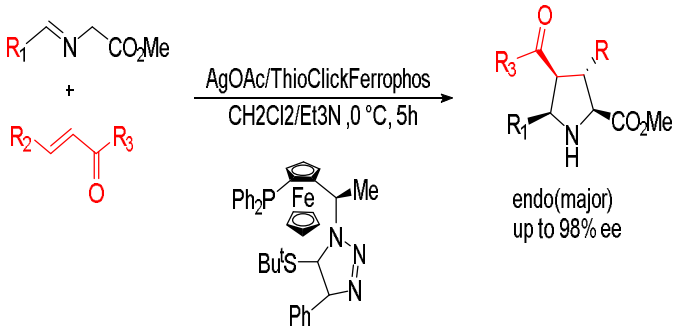
α-enones holds great synthetic potential[3] have scarcely been studied toward 1,3-cycloaddition as dipolarophile until Carretero[4] who first investigated the cycloaddtion of aryl amine of glycine methyl ester with acyclic α-enones showing exo-selectivity (*exo:endo=98:2)* and ee 96% for major product and endo-selectivity *(exo:endo=10:90)* cyclic enones (cyclopentanone) with ee 94% for endo product.

*c) 2. Copper catalyzed intermolecular carboamination:*A copper-catalyzed intermolecular carboamination of potassium N-carbamoyl-β-aminoethyltrifluoroborates with te rminal, 1,2-disubstituted, and 1,1-disubstituted
vinylarenes bearing a number of functional groups provides 2-arylpyrrolidines. 1,3-Dienes are also good substrates, and their reactio ns give 2-vinylpyrrolidines. C. Um, S. R. Chemler, Org. Lett., **2016**, 18, 2515-2518.



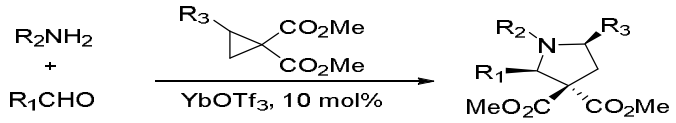
*d) Silver metal catalyzed reaction:*Oura et al.,[5] synthesize fuctionalized endo-4-acyl pyrrolidines through highly endo-selective asymmetric 1,3-dipolar cycloaddition of N-benzylideneglycinate (source of azomethine ylide) with (E)-acyclic α-enones. Reaction

was catalyzed by silver(I)thioclickferrophos to obtain endo major product(*endo:exo= 90:10—99:1)* in good yields with high ee upto 98%. Product obtained were contrast in selectivity to that synthesized by carretero Cu/fesulphos(exo major product) catalyst however when Ag(I)thioclickferrophos was used for cyclic α-enones product obtained shows same selectivity to that shown by cu/fesulphos (endo major product).conclusively Ag(I)thioclickferrophos catalyzes endo-selective 1,3cycloaddtion for both acyclic and cyclic α-enones.



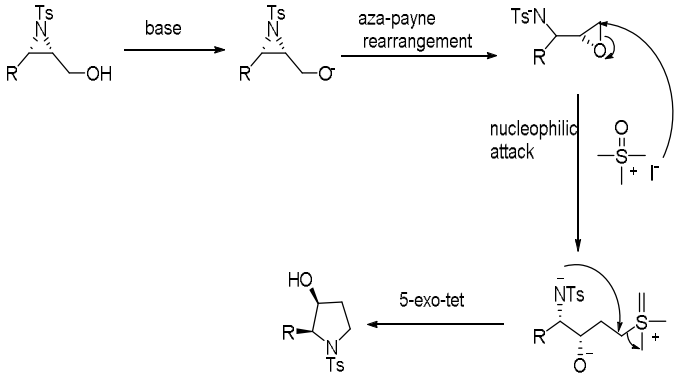
(1). Fukuzawa, N.I.; Oki, H. Org. Lett. 2008, 10, 1747-1750. (2). Fukuzawa,S.-i.; Yamamoto, M.; Hosaka, M.; Kikuchi, S. Eur. J. Org. Chem. 2007, 5540-5545. (3). Ruano, J. L. G.; Tito, A.; Peromingo, M. T. J. Org. Chem. 2003, 68, 10013–10019. (4).Herna´ndez-Torbio, J.; Arraya´s, R. G.; Martı´n-Mature, B.; Carretero, J. C. Org. Lett. 2009, 11, 393–396. (5) Oura, I.; shimizu, K.; ogata, k.; fukuzawa, S.I. Org. Lett. 2010, 12, 1752-1755.

*18) Multicomponent reaction of aldehyde, amine and 1,1-cyclopropanediesters catalyzed by ytterbium triflate::*Kerr et al.[1] have reported an efficient and stereo selective three component reaction of aldehyde, primary amine and 1,1-cyclopropanediester for production of N-alkyl , N-aryl pyrrolidine derivative. Process involves *in situ* generation of aldimines due to reaction between aldehyde and amine, intermediate formed undergoes smooth reaction with third reactant (1,1-cyclopropanediesters) mediated by $Yb(OTf)_3$ lewis acid catalyst. cis relationship exist between C-2 and C-5 substituent of major diastereoisomer product.

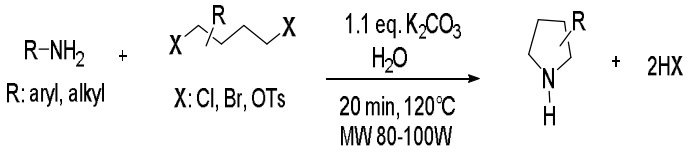


(1). Kerr, M.A.; Carson, C.A. *J. Org. Chem.* **2005**, *70*, 8242-8244.

*19) Via Aza-payne rearrangement :*Aza- payne rearrangement[1] of 2,3-aziridin-1-ols under basic condition favours formation of epoxy amines which on subsequent nucleophilic attack of epoxide by dimethyl sulfoxonium methylide gives a bis-anion. Latter upon 5-exo tet ring closure yield desired pyrrolidine product with fully translated stereochemistry as present in asymmetric aziridinol**.**

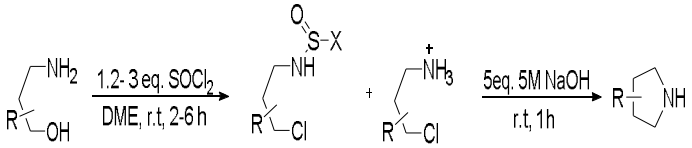


20) Microwave assisted N-hetrocyclization of primary amine with dihalide: Ju et al.,[2] reported one pot straight forward synthesis of nitrogen containing heterocycles from alkyl halide (ditosylates) and primary amines under microwave irradiation in alkaline aqueous medium via efficient dialkylation.



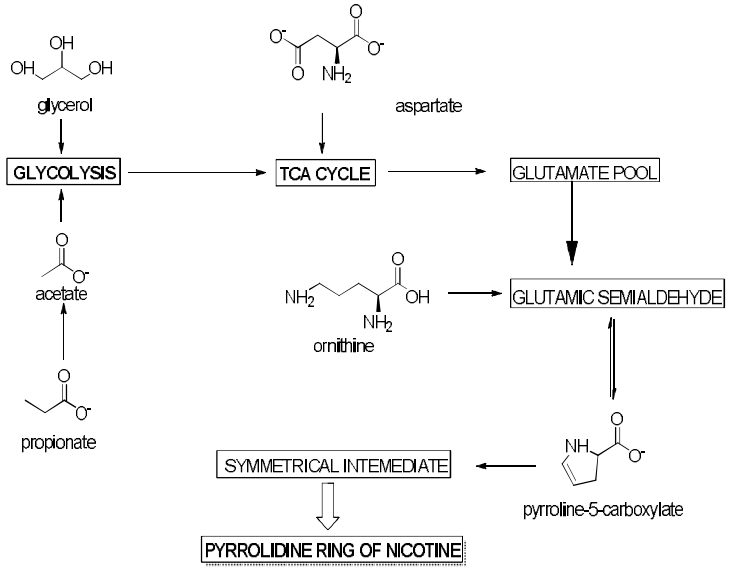
uses water as aqueous media in conjunction with microwave which shortens the reaction time, single step reaction to obtain high yields.

*21) via cyclohydration of amino alcohol :*Xu et al.,[3] investigated the simple one pot synthesis of efficient chlorination of amino alcohol with use of $SOCl_2$.



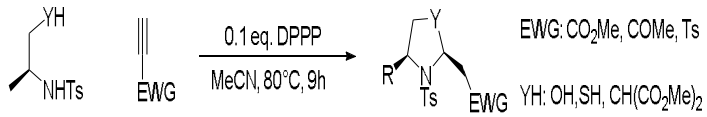
(1). Schomaker, J. M.; Bhattacharjee, S.; Yan, J.; Borhan, B. *J. Am. Chem. Soc.*, **2007**, *129*, 1996-2003.(2).Ju, Y.;. Varma, R. S. *J. Org. Chem.*, **2006**, *71*, 135-141.(3) Xu, F.; Simmons, B.; Reamer, R. A.; Corley, E.; Murry, J.; Tschaen. D. *J. Org. Chem.*, **2008**, *73*, 312-315.

22) Wu et al.,[1] disclosed the mechanism of pyrrolidine formation by feeding C^{14}-labelled acetate, propionate, glycerol and aspartate for different time period in nicotina rustica plant, which were utilized and converted via glycolysis and tricaboxylic acid cycle (TCA cycle) into glutamate ultimately leading to yield pyrrolidine via Δ^1-pyrroline-5-carboxylate and symmetrical intermediate conformed by C^{14} equally distributed between C-5 and C-2 of product pyrrolidine.

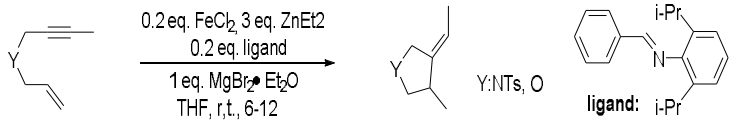


Formation of the pyrrolidine ring of nicotine in tobacco

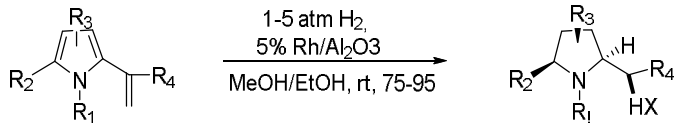
Sriramurthy et al.,[2] reported stereoselective synthesis of functionalized pyrrolidine in presence of bisphosphine catalyst via aminoacid derived pronucleophiles as Michael donor and electron deficient acetylenes as Michael acceptor.



*23) Reductive cyclization of enyne: :*Lin et al.,[3] reported simple iron catalyzed simple reductive cyclisation of N-tethered1,6-enynes into pyrrolidine enabled by discovery of unique combination of diethylzinc and magnesium bromide etherate which activates the pre catalyst $FeCl_2$ and bidentate imino pyridine ligand *in situ.*

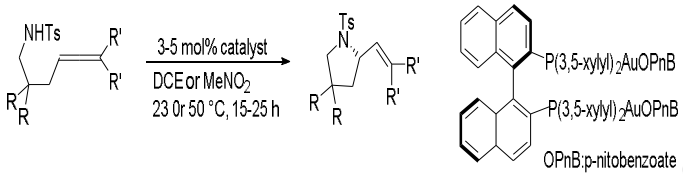


*24) By reduction of substituted pyrroles:*Fully functionalized pyrrolidine were derived via heterogeneous catalytic hydrogenation of substituted pyrroles in presence of 5% Rh/Al_2O_3. The reduction reaction resulted in excellent diastereoselectivity.[4]



(1).Wu,P.H.L.; Griffith, T.; Byerrum.R.Y. Jor.Biological. Chem.**1962**.237. (2).Sriramurthy, V.; Barcan, G. A.; Kwon, 0. J. Am. Chem. Soc. **2007**, 129, 12928.(3) Lin, A.; Zhang, Z.W.; Yang, J. Org. Lett., **2014**, 16, 386-389. (4) Jiang, C.; Frontier, A. J. Org. Lett. **2007**, 9, 4939.

*25) By cyclization of allenes :*Lalonde et al., reported enatioselective formation of vinyl pyrrolidine via asymmetric intramolecular hydroamination of allene catalyzed by phosphinegold(I)-bis-p-nitrobenzoate complex.



(1). Lalonde,R.L.; Sherry, B.D.; Kang, E.J.; Toste, F.D. *J. Am. Chem. Soc.*, **2007**, *129*, 2452-2453

C. Therapeutic potential of pyrrolidines

Substituted pyrrolidines are a pleiotropic molecule critical to a number of physiological and pathological processes. The last decade has witnessed major advances in dissecting pyrrolidine biology and its roleas anti-cancer, anti-microbial, anti-fungal, anti-mycobacterial, anti-viral and anti-diabetic agents.[63] Consequently, this molecule has become an attractive therapeutic target for drug development.[64] The pyrrolidines are useful molecular scaffolds for the exploration and exploitation of pharmacophore space which has led to the findings of new drug leads for the treatment of various diseases (Figure 3).

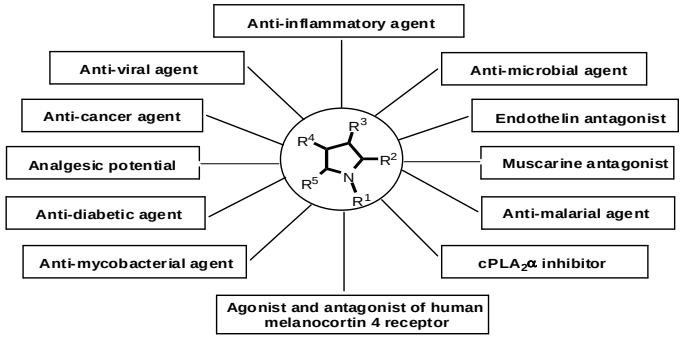


Figure 3. Biological activity of pyrrolidines

II. CONCLUSIONS AND PERSPECTIVES

Almost 2/3rd of all the known organic compounds belong to heterocyclic compounds, in particular, substituted pyrrolidines represent important key units or building blocks of numerous biologically active natural products and pharmaceuticals and therefore, this class of compounds has received significant attention by synthetic and medicinal chemist. Furthermore, its application in the synthesis of large number of chemotherapeutic agents such as antidiabetic, anticancer, antimalarial, antiviral, antimicrobial, anti-inflammatory and antibacterial agents as well as agonist and antagonist of endothelin and human melanocortin 4 receptor illustrate its importance in medicinal world. In addition, importance of chiral synthons in organic and medicinal chemistry is of imperative importance. The 1,3 DC reaction is one of the most powerful and successful synthetic tool for the construction of five membered pyrrolidine rings in regio- and stereoselective manner. More importantly, the reactions between azomethine ylides and activated alkenes afforded tetrasubstituted pyrrolidine in one step along with the four adjoining chiral centers. We believe that in future this heterocyclic motif will receive great attention in the field of medicinal chemistry and drug development and the progresses in synthetic methodology.

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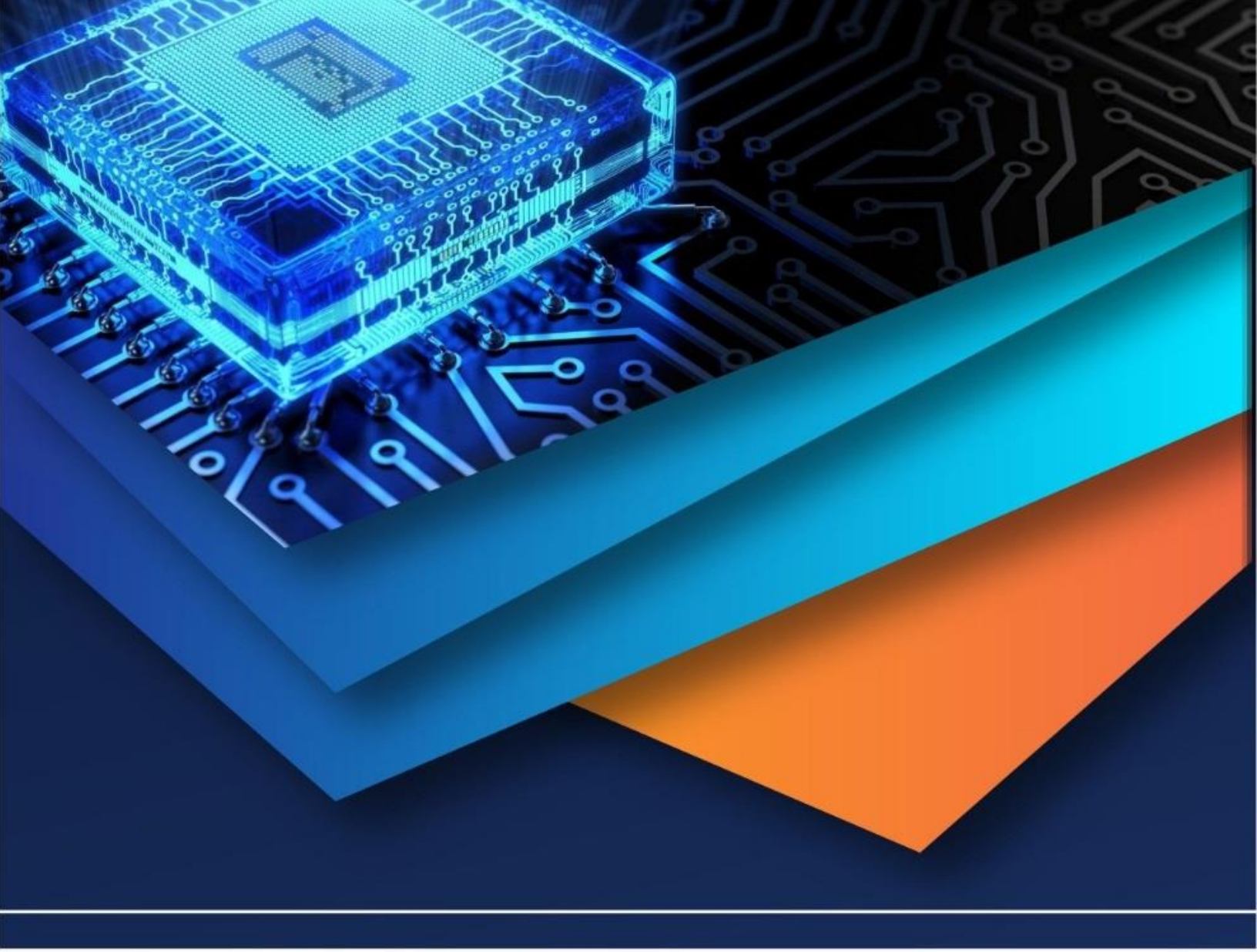

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