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ARTICLE TYPE

1,3-carbon D-A strategy for [3+2] cycloadditions/annulations with imines: Synthesis of functionalized pyrrolidines and related alkaloids†

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Cycloaddition/annulation reactions remain to be the most attractive methods for the synthesis of five membered heterocyclic ring systems. Among the three possible strategies for [3+2] cycloaddition, this review focuses on 1,3-carbon donor-acceptor (C3, D-A) cycloaddition/annulation reactions with imines to synthesize pyrrolidines. The formal [3+2] cycloaddition, which includes the in situ 1,3-carbon D-A precursor generation through metal catalysis, Lewis acid catalysis and organocatalysis approaches are highlighted. The scope and limitations of this strategy along with its applications in the synthesis of natural products alkaloids reported during last decade are outlined.

1. Introduction

Nitrogen heterocycles are probably the most representative group of heterocycles found in nature. Additionally, saturated nitrogen heterocycles such as pyrrolidines and piperidines are fundamental biological scaffolds present in a large number of natural and synthetic compounds. Particularly, pyrrolidines are important synthetic targets for chemists due to its great abundance in natural products,[1] wide applications as chiral ligands,[2] and its use as organocatalysts[3]. 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*'.[4] Conceptually, [3+2] cycloaddition/ annulation methods for pyrrolidine synthesis can be described in three possible ways (Figure 1):

(**A**) 1,3-dipolar cycloaddition between azomethine ylides (AMY) and activated alkenes (Path A, Figure 1).[5]

(**B**) [3+2] cycloaddition/annulation reaction between 1,3-cabon-nitrogen dipolar species and alkenes (Path B, Figure 1).[6]

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

Among the three methods, [3+2] cycloaddition/annulation through 1,3-carbon *donor-acceptor* (D-A) strategy 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. Despite of a notable progress, a comprehensive review in this direction is lacking in the literature. Considering the importance and attractiveness of this method, we would therefore like to present a survey in this direction.

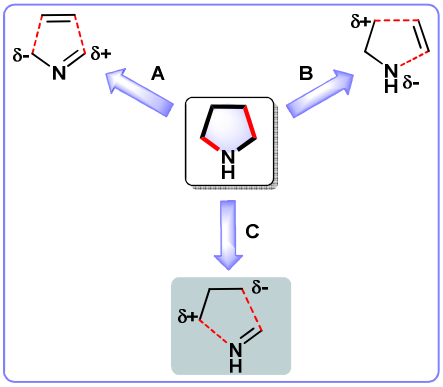

Figure 1: Possible routes for pyrrolidine synthesis through [3+2] cycloaddition/annulation reactions

The main focus of review will be to provide a complete overview on alternative approach through 1,3-carbon D-A cycloaddition/ annulation for pyrrolidine and related alkaloid synthesis. 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. The discussion excludes phosphine catalyzed *in situ* generation of 1,3-carbon dipole from substituted allenes, followed by cycloaddition with imines for the synthesis of pyrrolidines, as it has been documented recently.[7]

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 such as: (i) cyclopropane ring opening, (ii) Metal catalyzed

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†This article is dedicated to Dr. Vijay Nair (NIIST-CSIR) for his contribution in organocatalysis.

trimethylenemethane, and (iii) organocatalysis (Figure 2). In addition, the current review provides updated information on the application of this approach for the synthesis of related alkaloids.

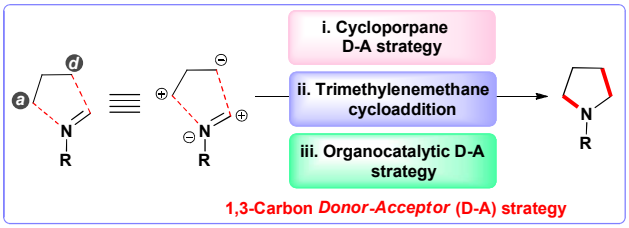


Figure 2: 1,3-Carbon D-A strategies for [3+2] cycloaddition/ annulation with imine

2. Cyclopropane D-A ring opening strategy

The usefulness of cyclopropane *donor–acceptor* (D-A) strategy is mainly defined by their reactivity in [3+n] cycloadditions and other transformations for alkaloid synthesis.[8] In particular, the formal [3+2] cycloaddition of D-A cyclopropanes with different dipolarophiles has emerged as most rational and straightforward synthetic route for the construction of various five-membered carbo- and heterocycles. These reactions involve *in situ* generation of 1,3-carbon dipoles, followed by addition to dipolarophiles that bear X=Y bonds.[9] The special features of the reactions include high atom economy as well as excellent regio- and stereoselectivities observed in the products. In this section, we present the ring opening of cyclopropanes as C3 precursor for formal [3+2] cycloaddition through D-A mechanism with C=N of imines for the synthesis of pyrrolidines as well as related complex alkaloids (Figure 4).

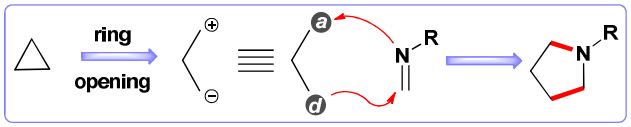


Figure 4: Cyclopropane D-A strategy for pyrrolidine synthesis

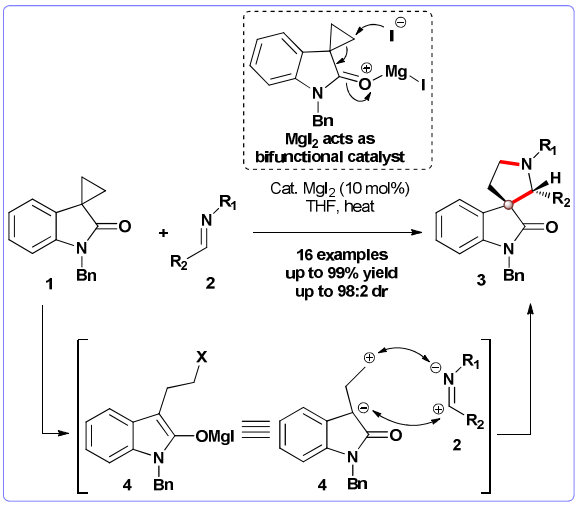
2.1. Lewis acid catalyzed ring opening of cyclopropanes

2.1.1. 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. Most of the [3+2] cycloadditions for the synthesis of pyrrolidines from strained cyclopropane derivatives and aldimines occurs through ring expansion strategy. 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.[10] 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-2,3'-oxindole] ring system **3** with high yields and selectivity (Scheme 1). These spiro[pyrrolidine-2,3'-oxindole] ring systems **3** are present in a number of compounds having biological importance.

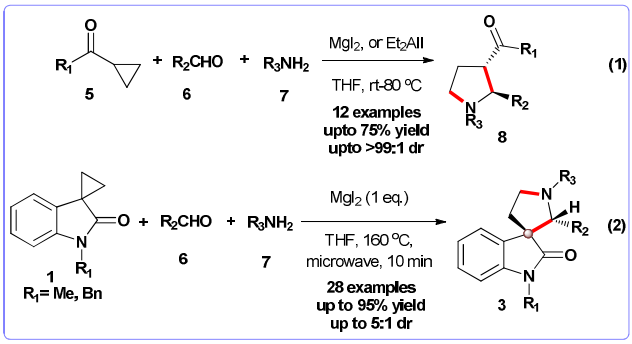
The unprecedented ring expansion is made possible by Magnesium Iodide (MgI_2) which acts as a bifunctional catalyst, in which the Lewis acidity of the metal center Mg^{+2} and nucleophilicity of the counter ion I^- appear to operate in synergy.

As shown in Scheme 1, ring opening of cyclopropane part of **1** by the catalyst would provide a reactive intermediate **4** that could engage an imine **2** in a nucleophilic or electrophilic capacity, that eventually provide ring expansion to spiro-pyrrolidines **3** as overall [3+2] annulation reaction. A variety of imines derived from aliphatic or aromatic aldehydes along with amine counterparts; aryl and alkyl amines, as well as sulfonamides were utilized under MgI_2-catalysis with complete tolerance.



Scheme 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).[11] This reaction proceeds through the similar mechanism as discussed in Scheme 1. 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.[12] The rapid synthesis of a library of **3** was achieved in shorter time period through stoichiometric use of MgI_2 (Eq. 2, Scheme 2).



Scheme 2: MgI_2 catalyzed ring expansion of cyclopropanes

The spiro[pyrrolidine-3,3'-oxindole] ring system **3** present in a number of alkaloids, possess significant biological activities and hence are interesting targets for chemical synthesis.[13] The Carreira group was successful in exploiting this synthetic strategy for the synthesis of various alkaloids (Scheme 3). The first application of [3+2] annulation of mono-activated

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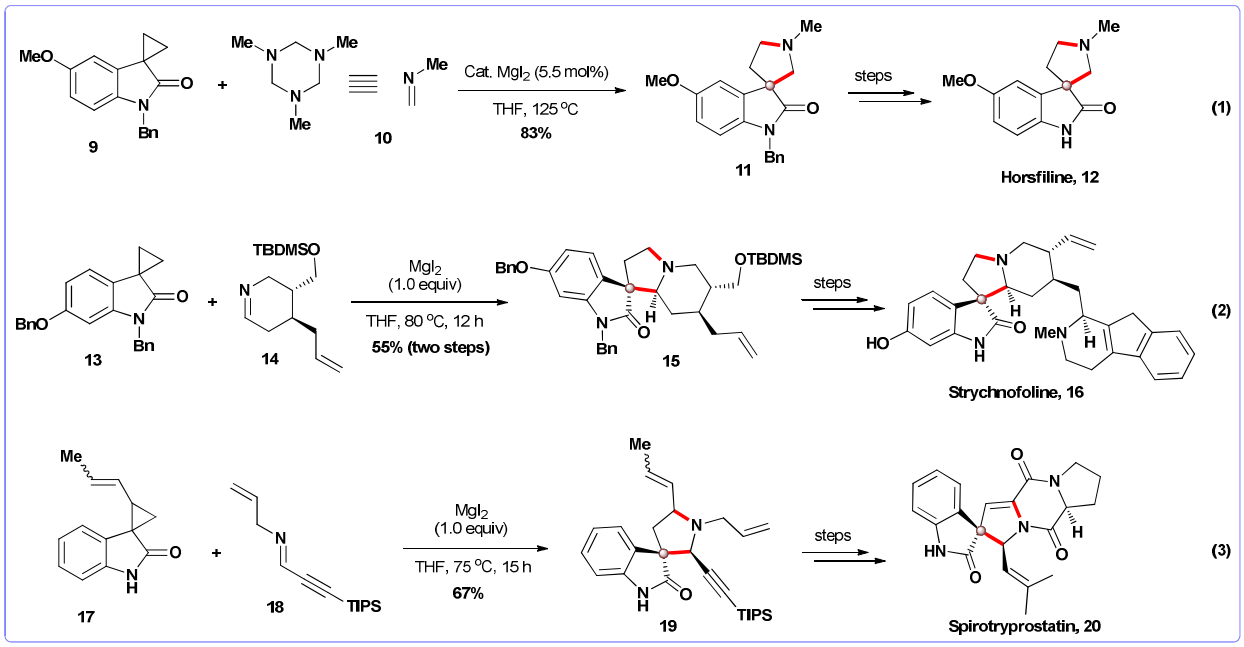
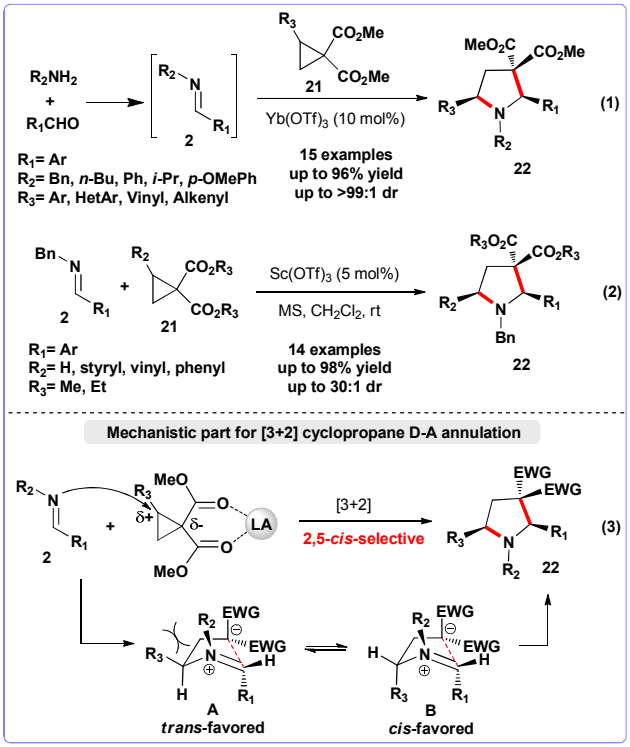


Scheme 3: Lewis acid ring expansion of cyclopropanes as [3+2] annulation in alkaloid synthesis

cyclopropane with imine was shown through the synthesis of (±)-horsfiline, a naturally occurring alkaloid.[14] The ring expansion of spiro[cyclopropan-1,3'-oxindoles] **9** with *in situ* generated imine **10** in the presence of MgI_2-catalytic system, furnished spiro[pyrrolidine-3,3,-oxindoles] **11**, which was easily converted to horsfiline **12** (Eq.1, Scheme 3). In a similar manner, the first total synthesis of the natural product (±)-strychnofoline **16**, was accomplished. The MgI_2-catalyzed [3+2] annulation reaction between spiro[cyclopropan-1,3'-oxindole] **13** and a cyclic imine **14** yielded fused spiro[pyrrolidine-3,3,-oxindole] **15** as a single diastereoisomer. This was subsequently converted into (±)-strychnofoline **16** (Eq. 2, Scheme 3).[15] The MgI_2 catalyzed [3+2] annulation strategy was further extended to the total synthesis of Spirotryprostatin **20**. The reaction between spiro[oxindole-3,1'-vinylcyclopropane] **17** and an alkynyl imine **18** produced spiro-pyrrolidine **19** as a 6:1 mixture of diastereomers with good yields. This spiro-pyrrolidine **19** was further utilized to complete the synthesis of **20** (Eq. 3, Scheme 3).[16]

2.1.2. Opening of 1,1-cyclopropanediesters

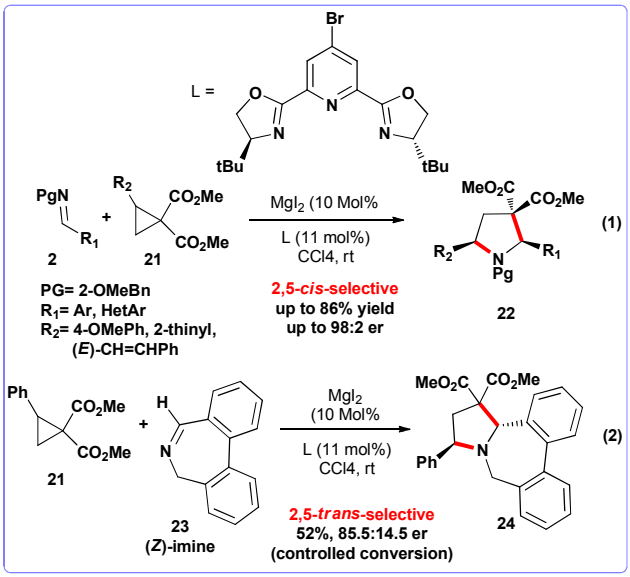
An alternative approach for the diastereoselective synthesis of densely substituted pyrrolidines through Lewis acid *viz,* $Yb(OTf)_3$ catalyzed ring opening of 1,1-cyclopropanediesters **21**, followed by [3+2] annulation with various *in situ* generated imines **2** was reported by Carson and Kerr (Eq. 1, Scheme 4).[17] Under optimized conditions, 2,5-*syn*-selective synthesis of substituted pyrrolidines **22** was achieved from preformed aldimines **2**, and 1,1-cyclopropanediester **21.** The *in situ* formation of aldimines cannot be utilized here because both aldehydes and amines are



Scheme 4: Lewis acid catalyzed [3+2] annulation for substituted pyrrolidines

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 **21** and various imines **2** was independently developed by Tang and coworkers (Eq. 2, Scheme 4).[18] The mechanism of the transformation was explained by the 1,3-carbon D-A strategy and the *syn*-diastereoselectivity can be attributed to the streic factors. Iminium-enolate zwitterionic intermediates **A** and **B** are formed by the S_N2 attack of imine **2** on activated cyclopropane ring under Lewis acid catalysis. The observed 2,5-*syn*-selectivity in **22** was explained *via* TS-**B**, preferably due to steric evidence at TS-**A** (Eq. 3, Scheme 4). Independently, 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.[19]

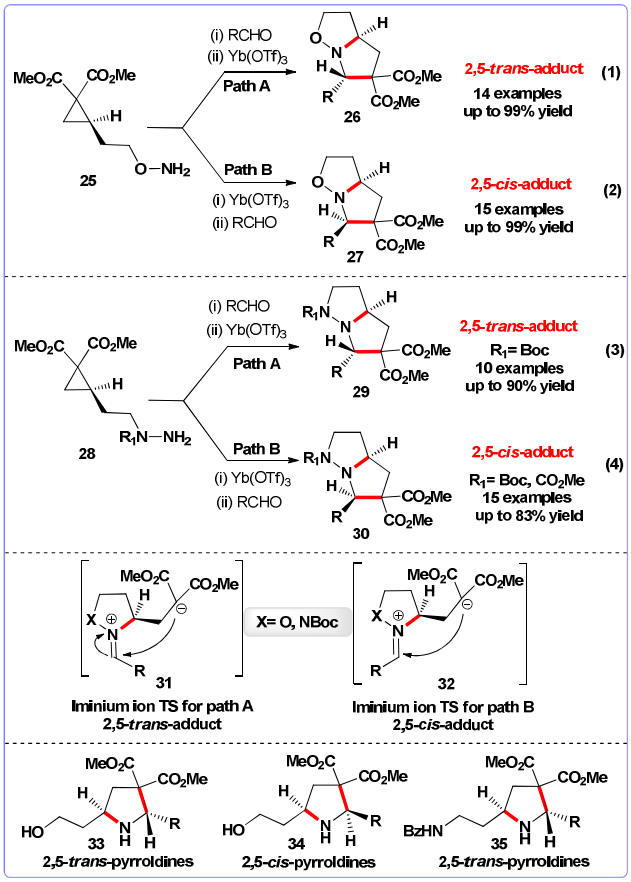
The enantioselective variant of [3+2] annulation involving ring opening D-A approach of 1,1-cyclopropanediesters **21** with imines **2** was recently developed by Johnson and co-workers.[20] They designed the first dynamic kinetic asymmetric transformation (DyKAT) of racemic **21** *via* chiral Lewis acid $(pybox)_2MgI_2$-catalyzed reaction with various (*E*)-imines **2** for the enantioselective synthesis of 2,5-*cis*-pyrrolidines **22** (Eq. 1, Scheme 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. This high level of selectivity was again explained through the envelope-type all equatorial transition state **B** (Eq. 3, Scheme 4), whereas low selectivity was observed in the case of 2,5-*trans*-pyrrolidine **24**, when (*Z*)-imine **23** was employed under similar reaction conditions (Eq. 2, Scheme 5).



Scheme 5: Cycloprrpane D-A [3+2] annulation in asymmetric manner

Kerr group developed $Yb(OTf)_3$ catalyzed stereospecific [3+2] annulation reaction of oxime ether-tethered cyclopropanediesters for the synthesis of enantiopure pyrrolo-isoxazolidines **26** and **27**, which served as precursor to the ubiquitous pyrrolidine motifs.[21] Interestingly, by simply altering the order of addition of aldehyde and catalysts to the same starting material **25** (Eq. 1 and 2, Scheme 6), the stereochemical outcome of the overall annulation reaction could be controlled. In Path **A** annulation proceeded through iminium-ion **31**, and 2,5-*trans*-substituted pyrrolidines are selectively formed, whereas the annulation proceeded through iminium-ion **32** in path B leading to the selective formation of 2,5-*cis*-substituted pyrrolidines.

Later on, this intramolecular [3+2] annulation strategy was further extended to the diastereoselective synthesis of complex fused bicyclopyrazolidines **29** and **30**, in a very similar manner (Eq. 3 and 4, Scheme 6).[22] 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 **28**. This intramolecular variant worked with improved reactivity as well as diasteroselectivity with a broad range of substrates allowing easy access to functionalized enantiopure pyrrolidines (**33**-**35**) by just cleaving the N-O, N-N bonds of [3+2] adducts.

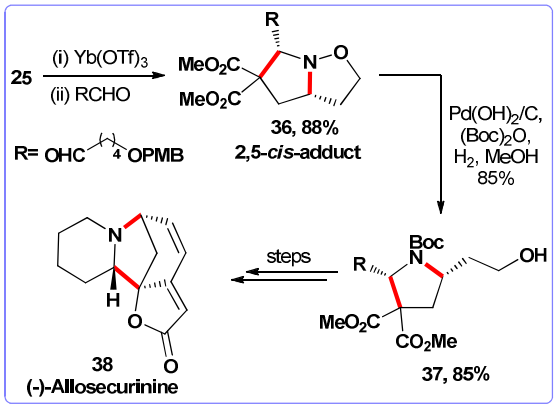


Scheme 6: Intramolecular cyclopropane D-A [3+2] annulation for fused pyrrolidines

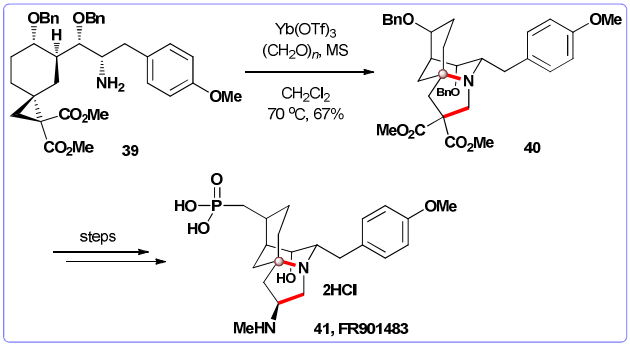
Intramolecular [3+2] annulation strategy for functionalized pyrrolidine synthesis utilized in the total synthesis of (-)-allosecurinine **38**, a *Securinega* alkaloid appears to be the first of that kind.[23] 2,5-*cis*-adduct **36** is obtained in high yield from **25** and well protected aldehyde by following the sequence of Path **B** (Eq. 2, Scheme 6). Adduct **36** was converted to funtionalized pyrrolidine **37** through N-O bond cleavage and subsequently to **38** (Scheme 7).

Further, the total synthesis of immunosuppressive alkaloid FR901483 **41** was developed *via* 1,1-cyclopropanediester

mediated intramolecular [3+2] annulation strategy.[24] The suitably designed amine-substrate **39** underwent $Yb(OTf)_3$ catalyzed ring expansion with *in situ* generated imine in the dilute solution of paraformaldehyde to furnish the tricyclic core **40**, which was subsequently converted to natural product FR901483 **41** (Scheme 8).

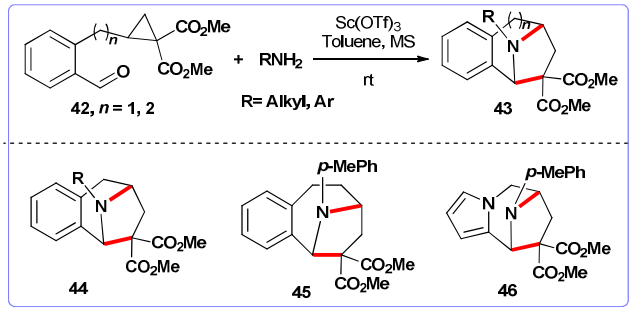


Scheme 7: Intramolecular [3+2] annulation application in the synthesis of (-)-Allosecurinine



Scheme 8: Total synthesis of FR901483 *via* intramolecular cyclopropane D-A [3+2] annulation

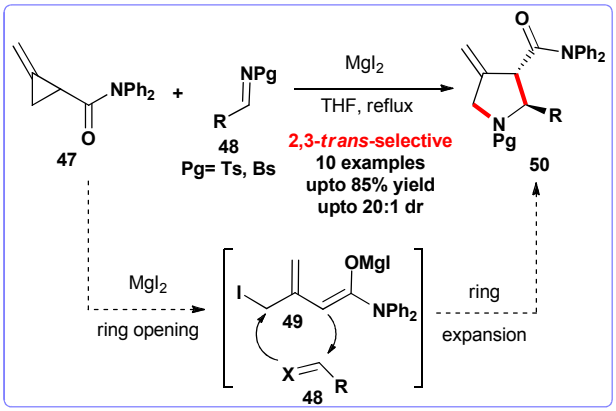
Recently, Wang and co-workers extended the scope of similar 1,1-cyclopropaediester D-A strategy in intramolecular [3+2] cycloaddition with *in situ* generated imine, for the synthesis of bridged bicyclic aza-[*n*.2.1] skeletons.[25] As shown in Scheme 9, suitably designed 1,1-cyclopropanediester **42**, enabled two component quick synthesis of azabicyclo[3.2.1] and azabicyclo[4.2.1] compounds under catalytic reaction conditions.



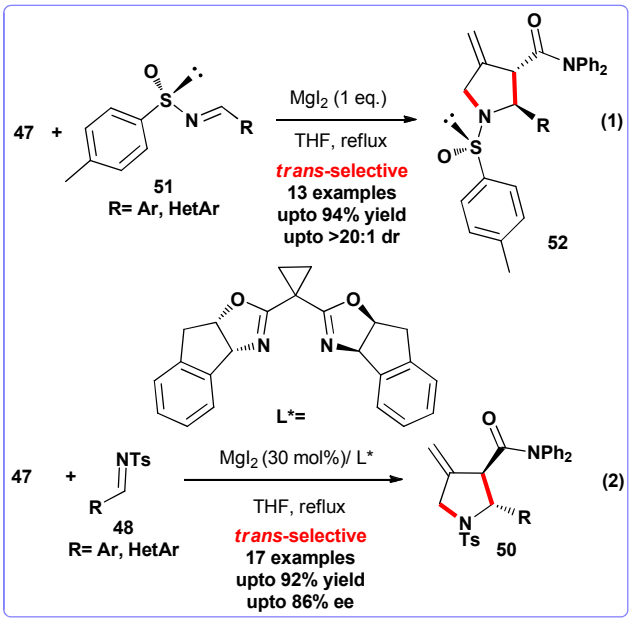
Scheme 9: Intramolecular [3+2] annulation for aza-bicyclo[n.2.1] skeletons

2.1.3. 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.[26] Inspired by the early report on MgI_2-mediated ring expansion of cyclopropanes from Carreira group,[10] 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 **47** with aldimines **48** in presence of MgI_2 was developed for methylene pyrrolidines **50** with high yields and *trans*-selectivity (Scheme 10).[27] This ring opening/cyclization strategy is expected to proceed through the ring opening of **47** with MgI_2, generating a vinylogous enolate intermediate **49**, bearing both nucleophilic and electrophilic sites within the same molecule. Subsequent reaction of the enolate **49** with aldimines **48**, followed by cyclization, *i.e.* an overall [3+2] annulation led to the formation of the corresponding 2,3-*trans*-pyrrolidines **50**.



Scheme 10: MCP-ring opening with MgI_2 and [3+2] annulation with imines



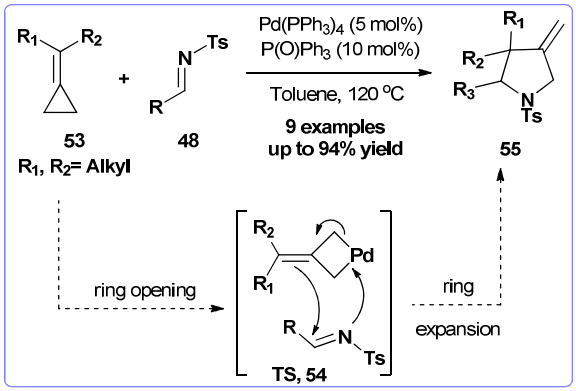
Scheme 11: Diastere- and enantioselective synthesis of pyrrolidines via [3+2] annulation of MCP

Later on, highly diastereoselective version of this MgI_2-

mediated [3+2] annulation strategy was developed by Lautens and coworkers.[28] In this strategy, chiral aromatic sulfinimines **51**, have been chosen based on the inference that they induce chirality for a variety of nucleophilic additions (Eq. 1, Scheme 11). Recently enantioselective [3+2] annulation of MCPs under chiral Lewis acid-MgI_2 catalysis was achieved by the same group.[29] As depicted in Eq. 2, Scheme 11, ring expansion of **47** in presence of *N*-tosyl aldimines **48** using chiral bis(oxazoline) lignad-MgI_2 complex amides provided direct access to enantio-enriched methylene pyrrolidines **50** with high yields.

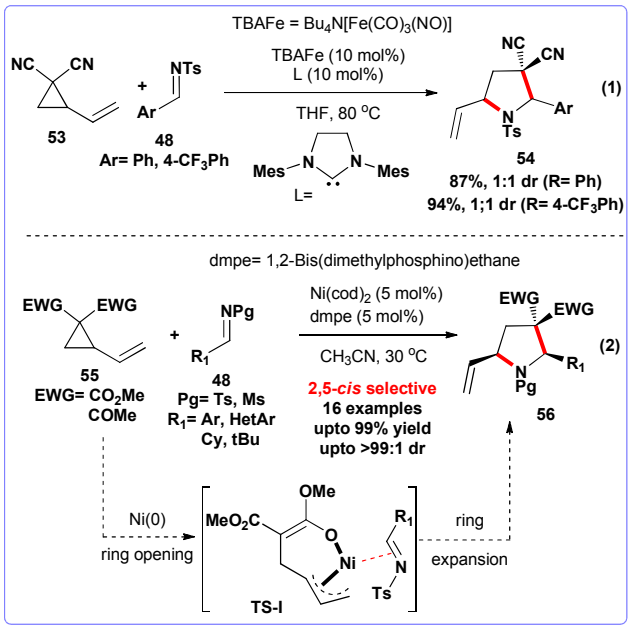
2.2. Metal catalyzed ring opening of cyclopropane

Metal catalyzed cycloaddition through the ring opening of cyclopropanes is a powerful method for the synthesis of cyclic systems.[30] 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) **53** with imines **48** reported by Yamamoto and co-workers can be considered to be the first of this kind.[31] The present atom-economical approach was explained through the reaction of **48** with palladacyclobutane complex (TS, **54**), followed by reductive elimination which furnished pyrrolidines **55** in high yields (Scheme 12).



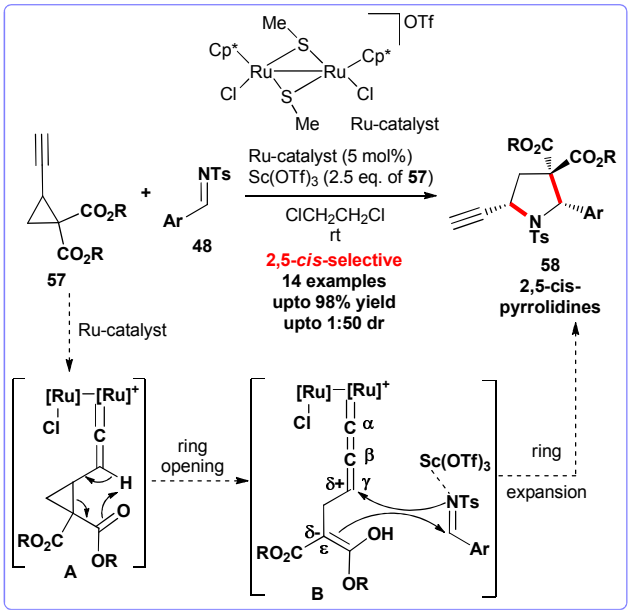
Scheme 12: Pd-catalyzed ring opening of MCPs for [3+2] cycloaddition with imines

Recently, Plietker and co-workers disclosed the pyrrolidine synthesis through the Iron-catalyzed ring opening of vinyl-cyclopropane **53**, followed by [3+2] cycloaddition with imines **48** (Eq. 1, Scheme 13).[32] 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 **54**. Additionally, Matsubara group also presented an analogous approach for substituted pyrrolidines by the Nickel-catalyzed [3+2] cycloaddition between vinyl-cyclopropane (VCP) **55** and imines **48**.[33] The diastereoselective [3+2] cycloaddition reaction proceed through the cyclic transition state TS-I formed by the coordination of imine to an oxa-nickel complex as shown in Eq. 2, Scheme 13.



Scheme 13: [3+2] cycloaddition *via* metal catalyzed ring opening of vinyl-cyclopropanes

Very recently, Nishibayashi and coworkers designed and developed a new ruthenium-catalyzed [3+2] cycloaddition reaction between ethynylcyclopropanes **57** with various aldimines **48** for the diastereoselective synthesis of substituted pyrrolidines.[34] 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 14). The presence of Lewis acid $Sc(OTf)_3$ is necessary to activate the aldimies 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 14: Ru-catalyzed alkynyl cyclopropane for [3+2] cycloaddition

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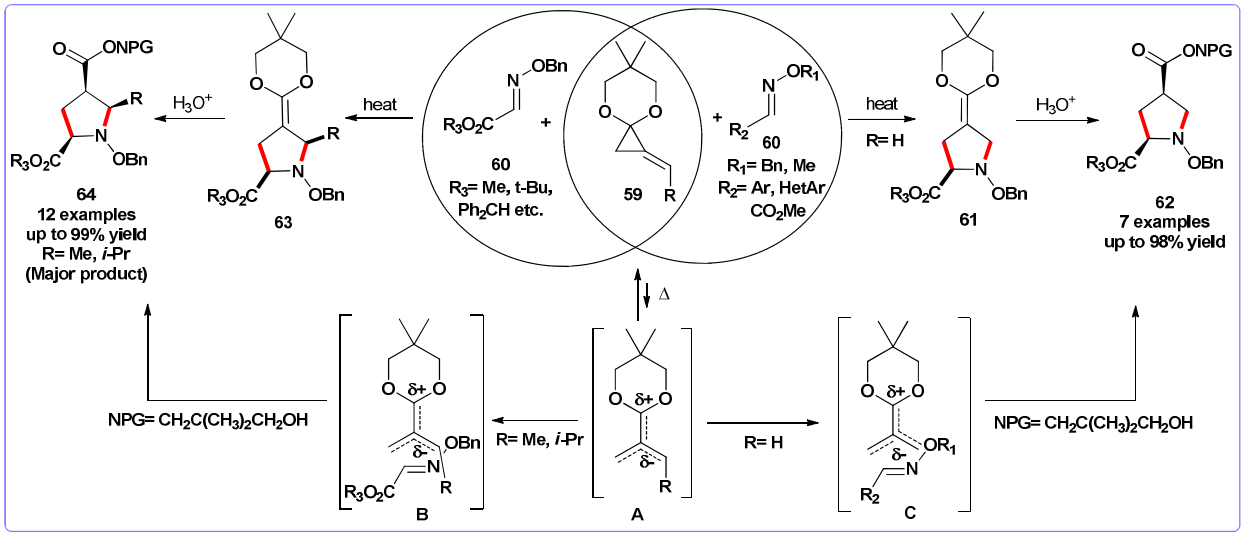


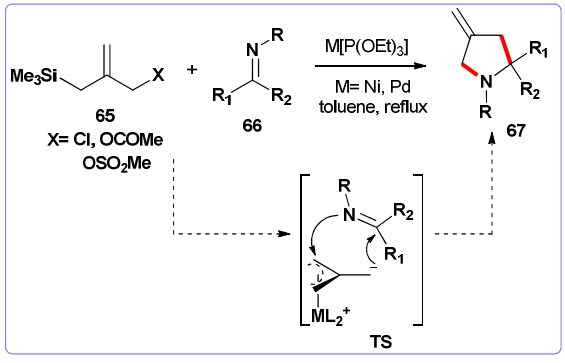
Scheme 15: [3+2] cycloaddition of TMMs under thermal conditions

3. [3+2] Cycloaddition through Trimethylenemethanes (TMMs)

3.1. Thermal Concerted [3+2] Cycloaddition

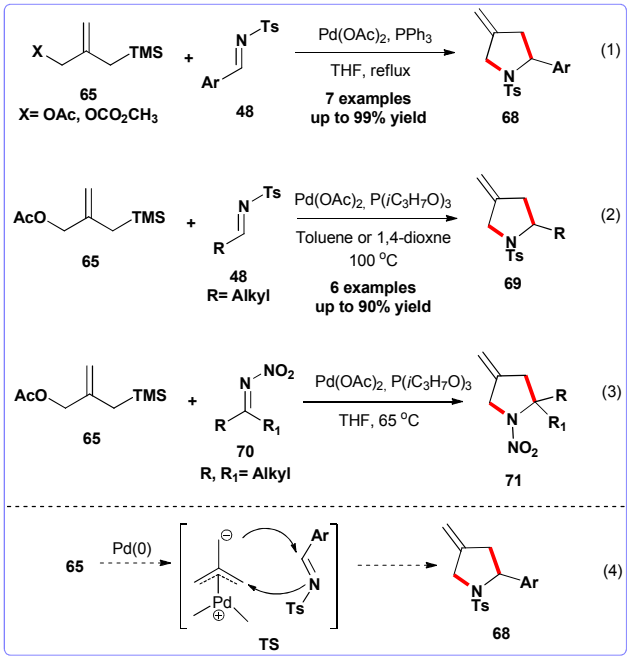
The thermal hetero [3+2] cycloaddition of dipolar trimethylenemethanes (TMMs) with *O*-alkyloximes was developed by Nakamura group.[35] The success of this reaction depended on the *in situ* reversible generation of the TMM species **A** from methylenecyclopropanes **59**. The TMM species **A** reacted with *anti*-O-alkyloxime **60** through a concerted mechanism to afford substituted pyrrolidines **62** and **64** with high regio- and stereoselectivities, whereas *syn*-O-alkyloxime failed to give similar transformation. Interestingly, bulky groups on the oxime directs the regio- and stereochemistry of this strategy as steric interaction control the oxime approach on to the 1,3-carbon dipole (**B**) and is responsible for the unequal ratio of products (Scheme 15).

3.2. Metal catalyzed [3+2] cycloaddition



Scheme 16: First metal catalyzed [3+2] cycloaddition of TMMs with imines

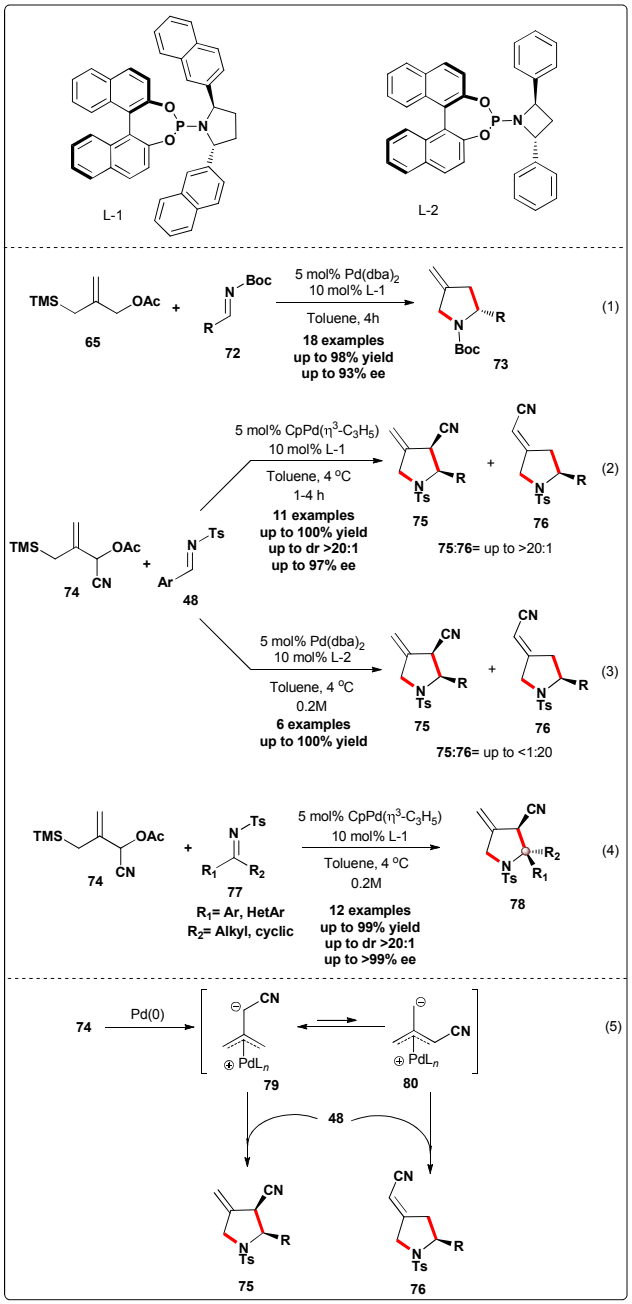
The first report on metal (Ni, Pd) catalyzed *in situ* generation of TMMs followed by [3+2] cycloaddition with various imines for one step synthesis of pyrrolidines was presented by Jones and Kemmitt (Scheme 16).[36]



Scheme 17: Pd-catalyzed [3+2] cycloaddition of TMMs

However palladium catalysed reactions developed by Trost group gave sufficient boost in this direction. The initial success on the two steps protocol for pyrrolidine synthesis using metal catalysis was reported independently from the groups of Trost and Klumpp.[37] Further a similar one step protocol involving

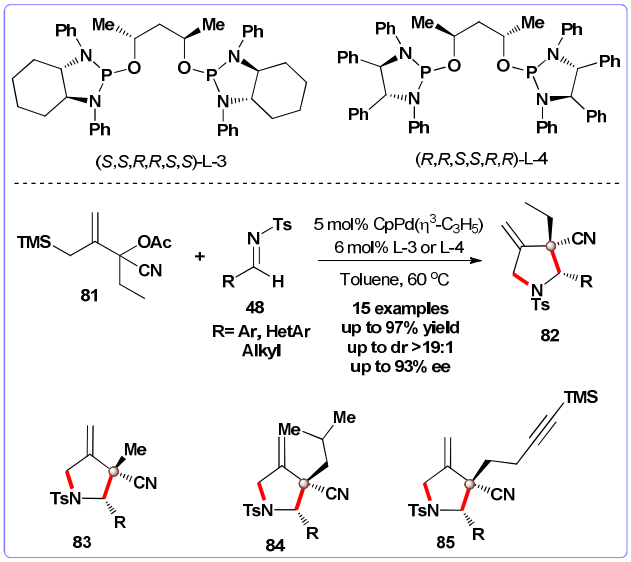
cycloaddition of TMMs with various imines was developed as detailed study in this direction.[38] Notably imines possessing an electron withdrawing group at either the carbon or nitrogen enhance the electrophilicity of imines, thus making it compatible for the reaction to occur, whereas simple imines fail to react under similar conditions. Imines derived from aromatic aldehydes (Eq. 1, Scheme 17) and aliphatic aldehydes (Eq. 2, Scheme 17) work efficiently for this [3+2] cycloaddition reaction in slightly different reaction conditions. Furthermore, nitro-imines **70**, a class of activated imines were explored for the first time in [3+2] cycloaddition with TMMs (Eq. 3, Scheme 17).



Scheme 18: Asymmetric and regio-selective [3+2] cycloaddition for substituted pyrrolidines

The first catalytic asymmetric version of palladium catalyzed [3+2] cycloaddition of trimethylenemethane with imines was developed in 2007.[39] In presence of chiral phosphoramidite ligand L-1, 3-acetoxy-2-trimethylsilylmethyl-1-propene **65** reacted with *N*-Boc imines **72** to furnish pyrrolidines **73** in high yields and excellent enantioselectivities (Eq. 1, Scheme 18). Having developed a practical route to the asymmetric synthesis of disubstituted *N*-Boc pyrrolidines, they turned their attention to substituted donors **74** with the goal of preparing more complex systems.[40] The facile reaction observed with tosyl imines **48** when studying the parent donor **65**, encouraged them to use **48** for substituted TMM donors **74**, as the steric bulkiness in substituted donor increased enantiodiscrimination and provided the desired product with a higher enantioselectivity.

Under developed conditions using electron-rich imines, a series of "normal" TMM cycloadducts such as **75** were obtained with high chemo-, diastereo-, and enantioselectivities along with a trace amount of the other regioselective product **76** (Eq. 2, Scheme 18). 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 exocyclic nitrile product **76** in high yields (Eq. 3, Scheme 18). Further study on Pd-catalyzed [3+2] cycloaddition of cyano–TMM donor with a series of tosyl ketimines **77** using CpPd(η^3-C_3H_5) and ligand L-1 were carried out successfully with excellent yields and enantioselectivities (Eq. 4, Scheme 18). The reaction is expected to proceed by the stepwise [3+2] cycloaddition reaction of π-allylpalladium species **79** and **80** generated *in situ* by ionization of the donor **74,** followed by acetate promoted desilylation, with imines **48** (Eq. 5, Scheme 18).[40]



Scheme 19: Asymmetric [3+2] cycloaddition for functionalized pyrrolidines bearing quaternary carbon

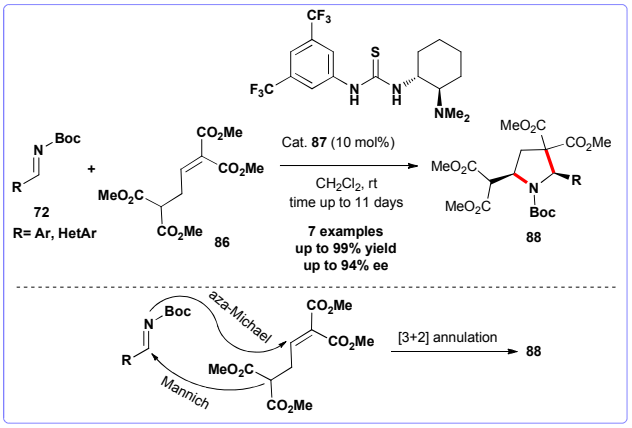
The use of disubstituted donor **81** for palladium-catalyzed trimethylenemethane [3+2] cycloaddition reaction with various *N*-Ts-imines **48** for the enantioselective synthesis of highly substituted pyrrolidines **82** is a recent development in this direction.[41] This [3+2] reaction furnished chiral pyrrolidines bearing quaternary centers when diamidophosphite ligands L3 and L4 were used. The reaction was also found to be general with variations in the alkyl substituents on the di-substituted TMM

donors and functionalized products having diverse architecture were formed in good yields and selectivities in all cases (Scheme 19).

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

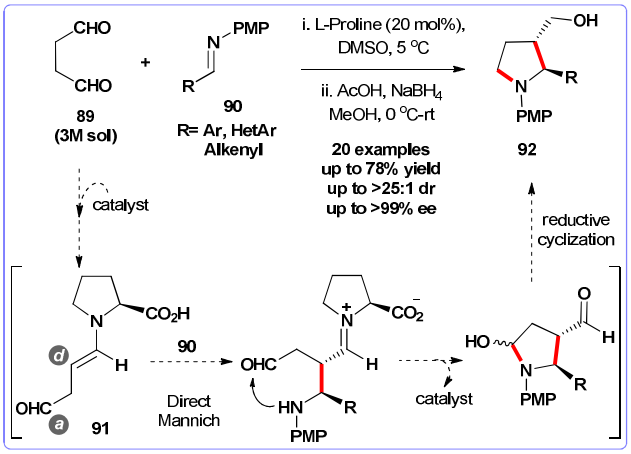
The development of organocatalysts has greatly changed the art of organic transformation in the in the past decade. The organocatalytic cascade reactions involving two or more selective transformations using single/multiple catalysis are now considered to be the most effective ways to design new catalytic asymmetric synthetic routes.[42] These reactions provide an easy way for the asymmetric synthesis of biologically active molecules and natural product motifs. Notably these reactions involve stereoselective bond formation which is a tremendous and enthusiastic strategy. Recently, organocatalysis have contributed significantly for 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 **86** with *N*-Boc arylaldimines **72** *via* [3+2] annulation for the synthesis of substituted pyrrolidines.[43] This new method catalyzed by bifunctional thiourea **87** furnished 2,5-*cis*-configured polysubstituted pyrrolidines **88** in excellent yields and enantioselectivities, however required long reaction time as shown in Scheme 20.



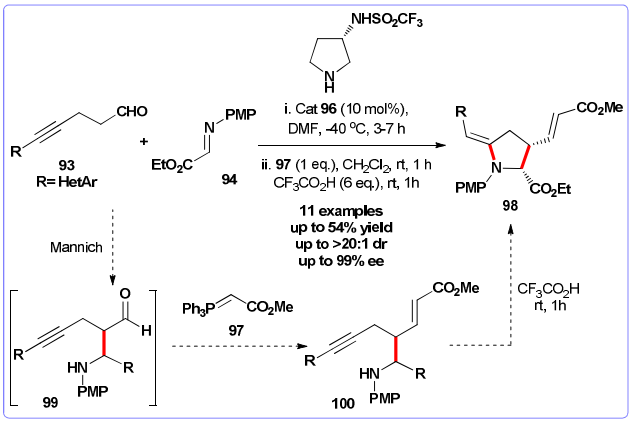
Scheme 20: Sequential Mannich/aza-Michael addition as [3+2] annulation reaction

Kumar and co-workers developed a very simple and highly stereoselective organocatalytic method for the synthesis of substituted pyrrolidines **92** from succinaldehyde **89** and *N*-PMP aldimines **90**.[44] The [3+2] annulation method involved, L-proline catalyzed direct Mannich reaction between **90** and *in situ* generated enamine **91** from linear dialdehyde **89** which serve as readily available 1,3-carbon D-A precursor, followed by acid catalyzed reductive cyclization (Scheme 21). 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 **92** with high yields and excellent enantioselectivities.



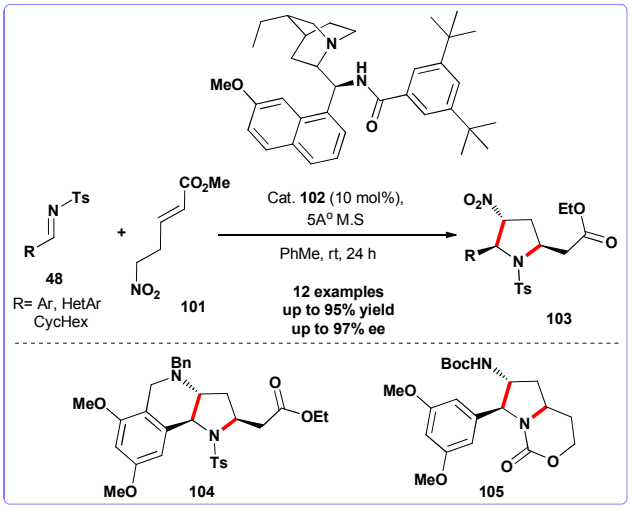
Scheme 21: Direct Mannich-reductive cyclization as [3+2] annulation for substituted pyrrolidines

De Paolis and co-workers recently developed another one-pot sequence of organocatalytic transformations for the synthesis of heteroarylmethylene-substituted pyrrolidines.[45] This reaction involved *anti*-Mannich coupling of *N*-heteroarylalkyne aldehydes **93** with aldimine **94**, followed by metal-free hydroamination *via* formal [3+2] annulation to deliver highly functionalized pyrrolidines **98** with very high selectivity (Scheme 22). The main feature of this approach is the use of alkynes connected to substitute *N*-heteroaromatics for the first time in organocatalytic transformations.



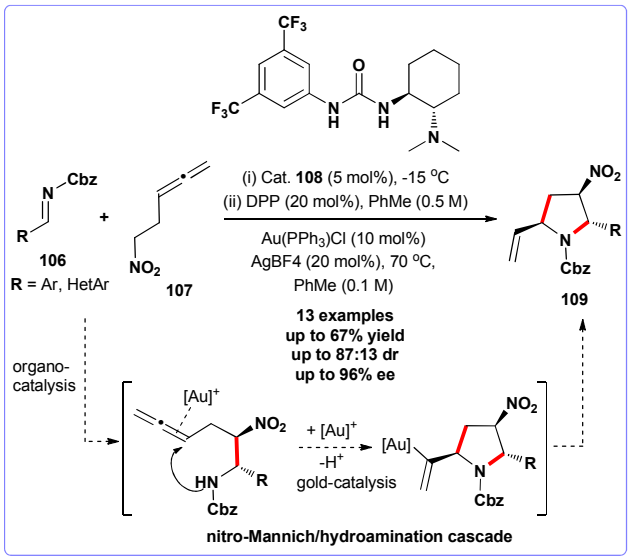
Scheme 22: Direct Mannich-metal free amination as [3+2] annulation for pyrrolidines

Cinchona alkaloid-derived organocatalyst **102** have recently been utilized by Huang and co-workers for the efficient synthesis of highly functionalized pyrrolidines **103**, with up to three stereogenic centers in high yields and enantioselectivities.[46] The [3+2] coupling of **48** with **101** involves a reversible aza-Henry reaction with a dynamic kinetic resolution (DKR)-driven aza-Michael cyclization. The highly functionalized products of this domino transformation were easily transformed into important synthetic skeletons **92**, **93** (Scheme 23).



Scheme 23: aza-Henry and DKR aza-Michael cascade reaction as [3+2] annulation for pyrrolidines

Dixon and co-workers reported a very similar diastereoselective base-metal catalyzed one-pot nitro-Mannich/hydroamination cascade strategy for substituted pyrrolidine synthesis.[47] Very recently, the same group developed asymmetric version of this cascade reaction for the synthesis of substituted pyrrolidines bearing three stereocentres.[48] The combination of bifunctional organocatalysis **108** and gold catalysis used in conjunction with *N*-Cbz imines **106** afforded pyrrolidines **109** in good yields with excellent enantioselectivities (Scheme 24).



Scheme 24: Organocatalyzed nitro-Mannich and gold-catalyzed hydroamination as [3+2] annulation

Conclusions and outlook

In the present review article, we have attempted to focus our attention on the synthesis of functionalized pyrrolidines through complementary [3+2] cycloaddition of 1,3-carbon D-A precursors and imines. The success of this strategy mainly rely on the availability of 1,3-carbon D-A precursor from readily available privileged scaffolds and on the fact that complex molecules could be generated in an efficient way. All three different modes of catalytic aspects such as, (a) *Lewis acid catalysis*, (b) *metal catalysis*, and (c) *organocatalysis*, have been extensively evaluated for this formal [3+2] cycloaddition approach. Special attention has been paid to the terminology concerning the 1,3-carbon D-A precursors, as designing of suitable 1,3-carbon D-A substrate is still important. Most of the catalytic approaches discussed here were restricted to the racemic version and the development of similar enantioselective transformations still remains challenging. However the recent metal catalyzed approaches from the Trost group and latest organocatalytic cascade transformations *viz*, [3+2] annulations were mainly in asymmetric mode. Even though it is underdeveloped with respect to other two methods for [3+2] cycloadditions; this 1,3-carbon D-A strategy has already been demonstrated to be of significant use in the synthesis of core ring systems of natural products, and of potential medicinal compounds. One can think of this approach as an exercise in designing of synthon that has the ability to stabilize 1,3-carbon D-A species *or* ability of a neutral compound to act as *in situ* D-A precursor. Indeed it is the interesting aspect of present [3+2] strategy that makes this method so appealing. We further assume that this review will make chemists cognizant to the synthetic potential of this fascinating strategy with limited 1,3-carbon D-A precursors. Much have already been understood, however activities towards the development of new type of cascade cyclization as formal [3+2] cycloadditions through this D-A strategy is anticipated in the near future.

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Notes and references

1. (*a*) J. R. Liddell, *Nat. Prod. Rep.*, 1999, **16**, 499. (*b*) D. O'Hagan, *Nat. Prod. Rep.*, 2000, **17**, 435. (*c*) K. Burgess and I. Henderson, *Tetrahedron*, 1992, **48**, 4045. (*d*) J. P. Michael, *Nat. Prod. Rep.*, 2005, **22**, 603. (*e*) F. C. Biaggio, A. R. Rufino, M. H. Zaim, C. Y. H. Zaim, M. A. Bueno and A. Rodrigues, *Curr. Org. Chem.*, 2005, **9**, 419.
2. (*a*) J. A. Sweet, J. M. Cavallari, W. A. Price, J. W. Ziller and D. V. McGrath, Tetrahedron: *Asymmetry*, 1997, **8**, 207. (*b*) F. Fache, E. Schulz, M. L. Tommasino and M. Lemaire, *Chem. Rev.*, 2000, **100**, 2159.
3. (*a*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719. (*b*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138. (*c*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2001, **40**, 3726.
4. (*a*) *Cycloaddition Reactions in Organic Synthesis*, ed. S. Kobayashi, and K. A. Jørgensen, Wiley-VCH, Weinheim, Germany, 2002. (*b*) K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2000, **39**, 3558. (*c*) P. Buonora, and J.-C. Olsen, T. Oh, *Tetrahedron*, 2001, **57**, 6099.
5. (*a*) A. Padwa and W. H. Pearson, *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*, Wiley, New York, 2002. (*b*) S. Husinec and V. Savic, Tetrahedron: *Asymmetry*, 2005, **16**, 2047. (*c*) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863..(*d*) C. Najera and J. M.

Sansano, *Angew. Chem., Int. Ed.*, 2005, **44**, 6272. (*e*) G. Pandey, P. Banerjee and S. R. Gadre, *Chem. Rev.*, 2006, **106**, 4484. (*f*) J. Adrio and J. C. Carretero, *Chem. Commun*., 2011, **47**, 6784. (*g*) P. Garner and H. U. Kaniskan, *Curr. Org. Synth*., 2010, **7**, 348. (*h*) W. H. Pearson, *Pure Appl. Chem.*, 2002, **74**, 1339.

6 (*a*) P. Restorp, A. Fischer and P. Somfai, *J. Am. Chem. Soc.* 2006, **128**, 12646. (*b*) M. A. Lowe, M. Ostovar, S. Ferrini, C. C. Chen, P. G. Lawrence, F. Fontana, A. A. Calabrese and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2011, **50**, 6370. (*c*) N. T. Jui, J. A. O. Garber, F. G. Finelli and D. W. C. MacMillan, *J. Am. Chem. Soc.* 2012, **134**, 11400. (*d*) G. Arena, C. C. Chen, D. Leonori and V. K. Aggarwal, *Org. Lett.*, 2013, **15**, 4250. For recent review, see (*e*) A. L. Cardoso and T. M. V. D. Pinho e Melo, *Eur. J. Org. Chem.* 2012, 6479 and references therein.

7 (a) For recent Review, see: (*a*) Q.-Y. Zhao, Z. Lian, Y. Wei and M. Shi, *Chem. Commun.*, 2012, **48**, 1724. (*b*) Y. C. Fan and O. Kwon *Chem. Commun.*, 2013, **49**, 11588.

8 For reviews on the D-A cyclopropanes reactivity, see: (*a*) H.-U. Reissig and R. Zimmer, *Chem. Rev.* 2003, **103**, 1151. (*b*) D. Agrawal and V. K. Yadav, *Chem. Commun.* 2008, 6471. (*c*) F. De Simone and J. Waser, *Synthesis* 2009, 3353. (*d*) P. Tan, and Y. Qin, *Synthesis*, 2012, 2969.

9 For recent reviews, see: (*a*) C. A. Carson and M. A. Kerr, *Chem. Soc. Rev.* 2009, **38**, 3051. (*b*) M. Ya. Mel'nikov, E. M. Budynina, O. A. Ivanova and I. V. Trushkov, *Mendeleev Commun*. 2011, **21**, 293. (*c*) Z. Wang, *Synlett* 2012, 2311. For recent cycloadditions to C=C and C=O bonds, see: (*d*) F. de Nanteuil and J. Waser, *Angew. Chem. Int. Ed.*, 2011, **50**, 12075. (*e*) X.-F. Xia, X.-R. Song, X.- Y. Liu and Y.-M. Liang, *Chem. Asian J.* 2012, **7**, 1538. (*f*) J.-P. Qu, Y. Liang, H. Xu, X.-L. Sun, Z.-X. Yu and Y. Tang, *Chem. Eur. J.* 2012, **18**, 2196. (*g*) Z. Luo, B. Zhou and Y. Li, *Org. Lett.* 2012, **14**, 2540. (*h*) B. M. Trost, P. J. Morris and S. J. Sprague, *J. Am. Chem. Soc.* 2012, **134**, 17823. (*i*) F. Benfatti, F. de Nanteuil and J. Waser, *Org. Lett.* 2012, **14**, 386. (*j*) G. Yang, Y. Shen, K. Li, Y. Sun and Y. Hua, *J. Org. Chem.* 2011, **76**, 229. (*k*) A. G. Smith, M. C. Slade and J. S. Johnson, *Org. Lett.* 2011, **13**, 1996. (*l*) S. Xing, Y. Li, Z. Li, C. Liu, J. Ren and Z. Wang, *Angew. Chem. Int. Ed.* 2011, **50**, 12605. (*m*) F. Benfatti, F. de Nanteuil and J. Waser, *Chem. Eur. J.* 2012, **18**, 4844.

10 P. B. Alper, C. Meyers, A. Lerchner, D. R. Siegel and E. M. Carreira, *Angew. Chem., Int. Ed.*, 1999, **38**, 3186.

11 F. Bertozzi, M. Gustafsson and R. Olsson, *Org. Lett.* 2002, **4**, 3147.

12 V. Helan, A. Mills, D. Drewry and D. Grant, *J. Org. Chem.*, 2010, **75**, 6693.

13 (*a*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem*., 2003, 2209. (*b*) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem*., 2012, **10**, 5165

14 C. Fisher, C. Meyers and E. M. Carreira, *Helv. Chim. Acta*, 2000, **83**, 1175.

15 (*a*) A. Lerchner and E. M. Carreira, *J. Am. Chem. Soc.* 2002, **124**, 14826. (*b*) A. Lerchner and E. M. Carreira, *Chem. Eur. J.* 2006, **12**, 8208.

16 (*a*) C. Meyers and E. M. Carreira, *Angew. Chem. In. Ed*., 2003, **42**, 604. (*b*) C. Marti and E. M. Carreira, *J. Am. Chem. Soc.* 2005, **127**, 11505.

17 C. A. Carson and M. A. Kerr, *J. Org. Chem.* 2005, **70**, 8242.

18 Y.-B. Kang, Y. Tang and X.-L. Sun, *Org. Biomol. Chem*., 2006, **4**, 299.

19 S. D. R. Christie, R. J. Davoile and R. C. F. Jones, *Org. Biomol. Chem.*, 2006, **4**, 2683.

20 A. T. Parsons, A. G. Smith, A. J. Neel and J. S. Johnson, *J. Am. Chem. Soc*. 2010, **132**, 9688.

21 S. K. Jackson, A. Karadeolian, A. B. Driega and M. A. Kerr, *J. Am. Chem. Soc*. 2008, **130**, 4196.

22 T. P. Lebold and M. A. Kerr, *Org. Lett*. 2009, **11**, 4354.

23 A. B. Leduc and M. A. Kerr, *Angew. Chem. In. Ed*., 2008, **47**, 7945.

24 C. A. Carson and M. A. Kerr, *Org. Lett.* 2009, **11**, 777.

25 S. Xing, W. Pan, C. Liu, J. Ren and Z. Wang, *Angew. Chem. In. Ed*., 2010, **49**, 3215.

26 M. Lautens, W. Klute and W. Tam, *Chem. Rev.* 1996, **96**, 49.

27 M. Lautens and W. Han, *J. Am. Chem. Soc*. 2002, **124**, 6312.

28 M. E. Scott W. Han, and M. Lautens, *Org. Lett*. 2004, **6**, 3309.

29 C. Taillier and M. Lautens, *Org. Lett*. 2007, **9**, 591.

30 A. Brandi, S. Cicchi, F. M. Cordero and A. Goti, *Chem. Rev*. 2003, **103**, 1213.

31 B. H. Oh, I. Nakamura, S. Saito and Y. Yamamoto, *Tetrahedron Lett*. 2001, **42**, 6203.

32 A. P. Dieskau, M. S. Holzwarth and B. Plietker, *J. Am. Chem. Soc*. 2012, **134**, 5048.

33 R. Tombe, T. Kurahashi and S. Matsubara, *Org. Lett*. 2013, **15**, 1791.

34 Y. Miyake, S. Endo, T. Moriyama, K. Sakata and Y. Nishibayashi, *Angew. Chem. In. Ed*., 2013, **52**, 1758.

35 (*a*) S. Yamago, M. Nakamura, X. Q. Wang, M. Yanagawa, S. Tokumitsu and E. Nakamura, *J. Org. Chem.* 1998, **63**, 1694. (*b*) S. Yamago, M. Yanagawa and E. Nakamura, *Chem. Lett.* 1999, **28**, 897.

36 M. D. Jones and R. D. W. Kemmitt, *J. Chem. Soc. Chem. Commun.* 1986, 1201.

37 (*a*) B. M. Trost and P. J. Bonk, *J. Am. Chem. Soc.* 1985, **107**, 1778. (*b*) J. Van der Leuw, J. L. Van der Baan, H. Scholter, G. J. J. Out, F. Bickelhaupt and G. W. Klumpp, *Tetrahedron Lett.* 1988, **29**, 3579.

38 B. M. Trost and C. M. Marrs, *J. Am. Chem. Soc*. 1993, **115**, 6636.

39 B. M. Trost and S. M. Silverman, J. P. Stambuli, *J. Am. Chem. Soc*. 2007, **129**, 12398.

40 B. M. Trost and S. M. Silverman, *J. Am. Chem. Soc*. 2012, **134**, 4941.

41 B. M. Trost, T. M. Lam and M. A. Herbage, *J. Am. Chem. Soc*. 2013, **135**, 2459.

42 For the recent reviews, see: (*a*) Ł. Albrecht, H. Jiang and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 8492. (*b*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*c*) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237.

43 D. Enders, D. P. Goddertz, C. Beceno and G. Raabe, *Adv. Synth. Catal*. 2010, **352**, 2863.

44 I. Kumar, N. A. Mir, V. K. Gupta and Rajnikant, *Chem. Commun*. 2012, **48**, 6975.

45 A. Jean, J. Blanchet, J. Rouden, J. Maddaluno and M. De Paolis, *Chem. Commun.* 2013, **49**, 1651.

46 T. Cheng, S. Meng and Y. Huang, *Org. Lett.* 2013, **15**, 1958.

47 A. Ďuriš, D. M. Barber, H. J. Sanganee and D. J. Dixon, *Chem. Commun.* 2013, **49**, 2777.

48 D. M. Barber, A. Ďuriš, A. L. Thompson, H. J. Sanganee and D. J. Dixon, *ACS Catal*., 2014, **4**, 634.

1,3-carbon D-A strategy for [3+2] cycloadditions/annulations with imines: Synthesis of functionalized pyrrolidines and related alkaloids

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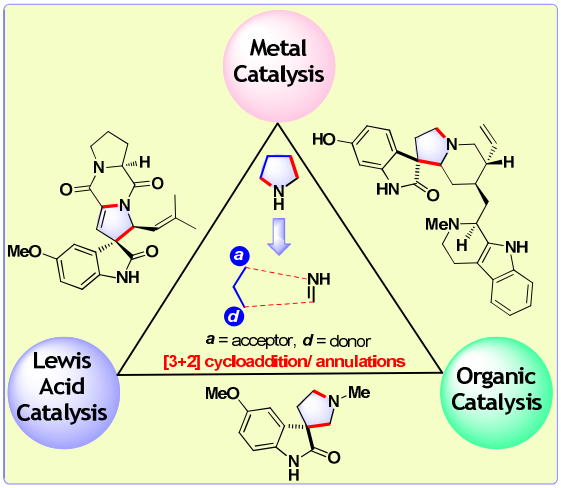

[3+2] cycloaddition/annulation: This article summarize the recent developments for synthesis of pyrrolidines and related alkaloids through complementary [3+2] cycloaddition/annulation of 1,3-carbon D-A precursors with imines.

Key words: cycloaddition, metal catalysis, Lewis acid catalysis, organocatalysis, cascade reactions, pyrrolidine.