Role of Metal Catalysts in the Conia-ene Reaction: Mechanism and Applications

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Abstract: Conia-ene reaction, an intramolecular addition of enols to alkynes or alkenes, has witnessed a lot of progress, and some interesting catalytic protocols responsible for milder reaction conditions have emerged. Conia-ene reaction is a beneficial reaction in organic synthesis due to its high atom economy and efficiency. In this review, mechanism and applications of recent advances in the metal-catalysed Conia-ene reaction is discussed.

Index Terms: Conia-ene reaction, metal catalysis, intramolecular addition, atom economy, concerted mechanism

I.INTRODUCTION

The formation of C-C bonds in organic chemistry is a very valuable entity and hence it has always attracted the attention of researchers. Over the years, many different methods have been devised to synthesize the C-C bond as it forms an integral part of organic syntheses. In recent times, exploration of such new approaches also focuses on other aspects such as generation of minimum waste, high atom economy with either good or excellent yields. To circumvent the drawbacks reported in earlier syntheses and to make the reaction greener, viable and environment friendly, research in this direction has gained tremendous momentum. In that regard, it has been found that pericyclic reactions fulfill most of the above-discussed criteria and hence they have been extensively studied for C-C bond formations taking place through concerted mechanisms. On a similar note, it may be emphasized that Conia-ene reactions also take place through a concerted mechanism. An ene reaction is an intramolecular or intermolecular organic reaction which occurs on an olefin substrate containing an allylic hydrogen and an electron withdrawing group **(Fig. 1)**. Such C-C bond formations take place with a high rate of atom economy.

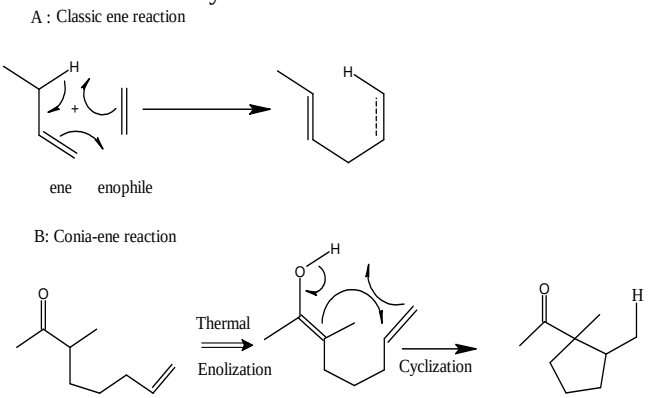
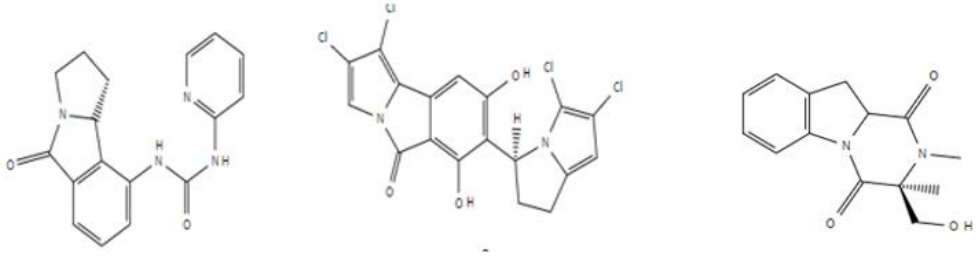


Figure 1: Classic ene reaction and Conia ene reaction

The Conia ene reaction was first introduced by Conia and Le Perchec in 1975 [1] involving intramolecular thermal cyclization of an unsaturated carbonyl compound which proceeds with high atom economy. Hence it is mostly used as a one-pot organic syntheses. Its synthetic utility lies in the syntheses of 5-9 membered heterocyclics [2,3] as well as carbocycles with high chemo-, regio-, and stereoselectivity [4,5]. It is used in the synthesis of tetrahydropyrroloindololone and its derivatives which form the core structure of many natural products, pharmaceuticals and biologically active molecules for example, (R)-1-(5-oxo- 2,3,5,9b-tetrahydro-1H pyrrole [2,1-a] isoindole-9-yl)-3-(pyridine-2-yl) urea, **A (Fig. 2**), [5] and (-)-chlorizidine, **B (Fig. 2),** [6]. Natural products containing both indoline and diketopiperazine, **C** [Figure 2], [7] moieties have very high potential bioactivity such as antifungal, antibacterial, antitumor, antiviral and antihyperglycemic.



A B C

Figure 2: Core structures in biologically active compounds

In the conventional Conia -ene reaction **(Fig. 1)**, the thermal condition required for the enolization process is approx. 200° to 300° C, particularly for the formation of 5- and 6-membered carbocycles. The use of such high temperatures presents a drawback with respect to thermo-labile compounds. An attempt to optimize such harsh conditions led to the search for the use of metal catalysts as Lewis acids so as to make the reaction work under milder conditions **(Fig.3)**.

This review mostly discusses the syntheses of five-membered exo- and endo-cyclic rings via the Conia-ene reaction using different metal catalysts. It also discusses the mechanistic route and applications of these reactions using varied metal catalysts.

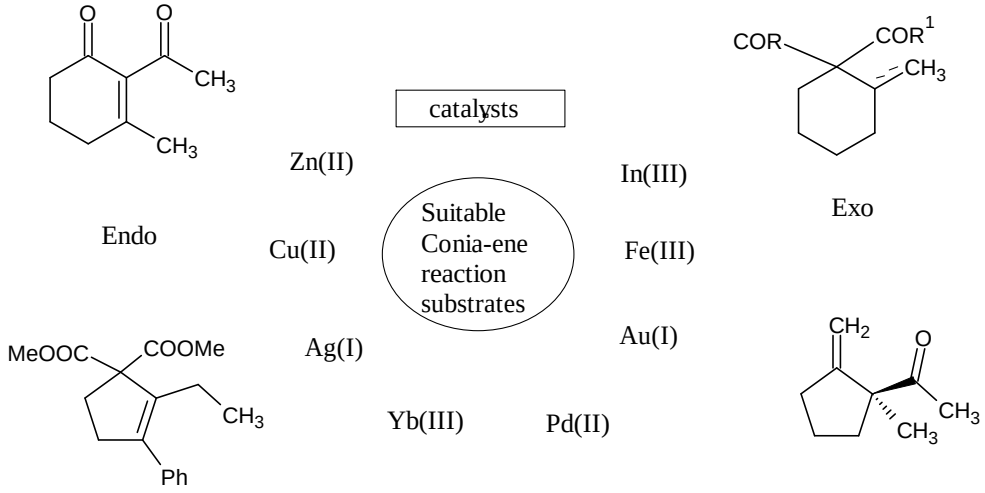
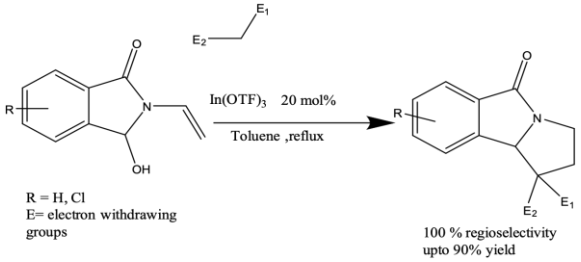


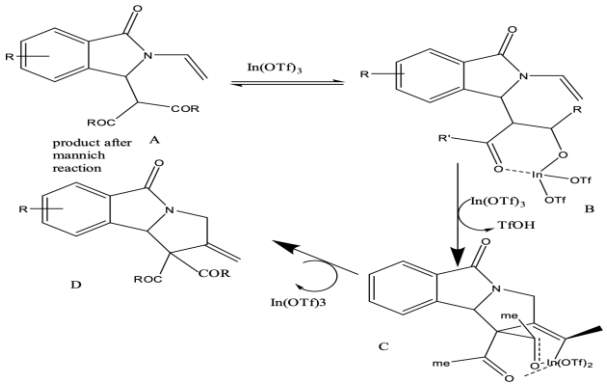
Figure 3: Metal Catalysts in Conia-ene reactions

1.0 Indium as catalyst

Sahu et al. developed a methodology for the synthesis of substituted tetrahydro pyrrolo isoindolone via Mannich reaction followed by Conia-ene using indium triflate as catalyst [8] **(Scheme 1 & 2)**. The reaction is highly regioselective with an exo-cyclic double bond in the pyrrolidine ring. The aza-Conia-ene cyclisation is also used for the synthesis of indolizine [9], wherein for the synthesis of the aza bicyclic compound a cyclic ion N-acyliminium ion is found to be beneficial [10].



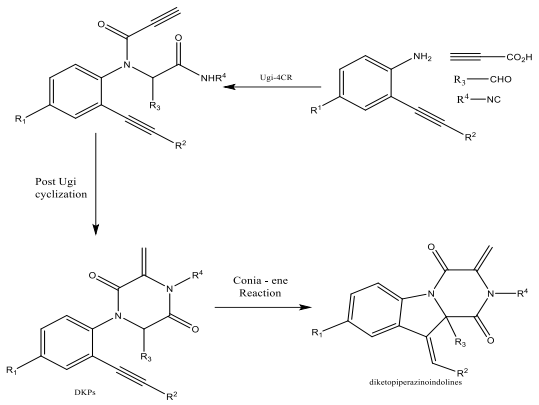
Scheme: 1



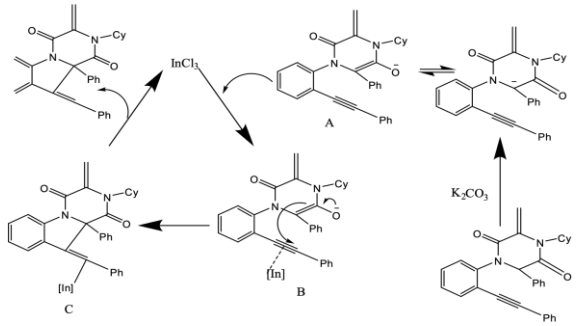
Scheme : 2 Possible mechanism

1.1 Diketopiperazines in Lewis acid-catalysed Conia-ene reaction

Recently Tejeneki et al. reported an efficient synthesis of diketopiperazines using phosphine-catalysed cyclisation of nitrogen-substituted 2-alkynamide whereby the DKPs formed undergo sequential Ugi-transformation reaction[11]. Further, the same group came up with an idea to employ ortho-alkynyl diketopiperazines in Lewis's acid-catalysed Conia-ene reaction for cyclisation wherein they reported Z-selectivity. Such high degree of selectivity is due to the π-π interaction between aryl groups in the product formed. **(Scheme 3 & 4)**



Scheme: 3

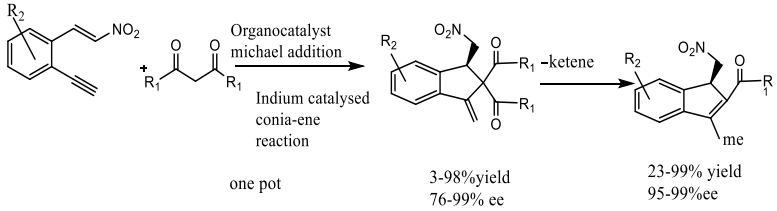


Scheme: 4 Possible reaction mechanism

In this process, indium trichloride (20 mol%) is used as a catalyst in 1.1 molar equivalent using MeCN as solvent at a temperature of 80 ℃ for 18 hours with 91% yield. Use of toluene as a solvent however, reduces the yield much lower to only 81%. This is probably because a polar solvent increases the stability of the ionic intermediates formed. The reaction is however unaffected by the presence of either EWG or EDG, both yielding comparably good results with Z diastereoselectivity [12].

1.2 Combination of organocatalysis and transition metal catalysis

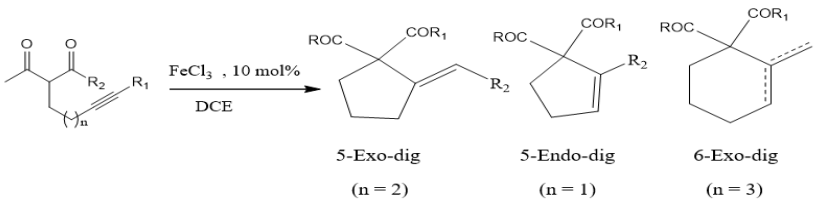
Recently, a researcher used a combination of organocatalysis and transition metal catalysis [13]. Before this, there has been only one example of asymmetric organocatalysis/Conia-ene sequence using indium salt as a metal catalyst [14]. Philipps et al. developed a novel method utilizing an enantioselective organocatalyst. In this synthesis (Scheme 7), the organocatalyst helps to combine a dicarbonyl compound with 2-ethynyl--nitrostyrene where the cyclization takes place using indium salt as catalyst via Conia-ene reaction. The yield of this one-pot synthesis depends upon the nature of the dicarbonyl compound [15,16]. Quinine shows the best asymmetric induction with 98% ee and a good yield of 92% (Michael reaction). Use of a lower concentration of catalyst had a beneficial effect on the stereoselectivity. In this reaction, DCE is used as solvent at room temperature for two hours for the Michael reaction followed by use of indium triflate in 10 mol %, toluene as solvent, at 80℃ for 3 hours [17] **(Scheme 5)**



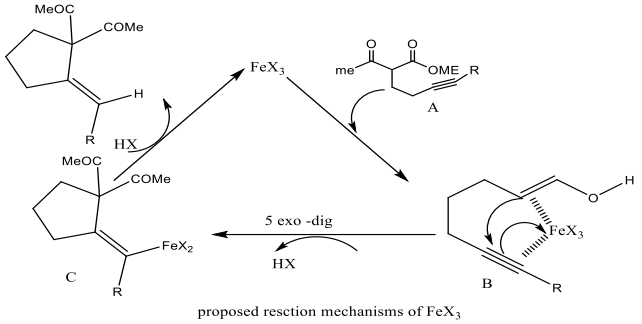
Scheme: 5

2.0 Fe (III) catalyzed Conia-ene reaction

Many transition metals are used for intramolecular cyclisation, primarily iron catalysts [18,19] as iron salt is naturally abundant, cheap, and easy to handle, having a low toxicity. In 2012, Chan et al. used anhydrous 10 mol % of $FeCl_3$ stirring with 2ml of DCE and the reactant carrying the 1,3-dicarbonyl group. The reaction is either stirred at room temperature or heated to a respective temperature and thereby a 5-exocyclo compound is synthesized. According to these researchers, 5- endo and 6-exo cyclisation are also possible depending upon the substrate [20] **(Scheme 6 and 7)**. In the above method, the authors have not thrown any light on the stereochemistry of the product. But in 2014, Shaw and White carried out enantioselective Conia-ene carbocyclization. It was seen that if the substrate is asymmetric in nature, then the utility of the reaction is enhanced. A chiral Fe (III)-salen complex is used for the asymmetric substrate with good yield and high ee%. The reaction does not require a co-catalyst. The R configuration of the product is obtained because the si face is blocked by the bulky salen ligands. In most of the cases, exo-methylene cyclopentane is formed in 90% yield and 90% ee. This method is not good for the synthesis of strained ring compounds [21] **(Figure 8 and 9)**.



Scheme: 6



Scheme: 7

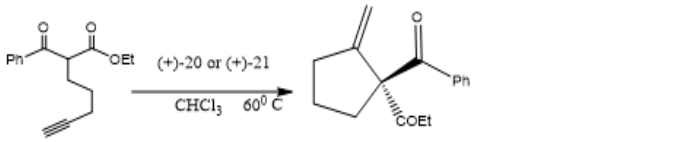


Figure: 8

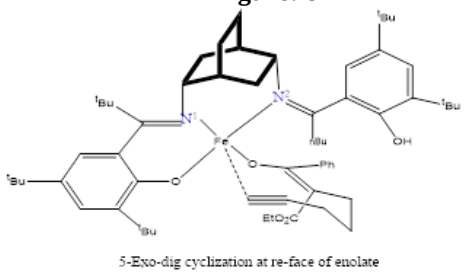
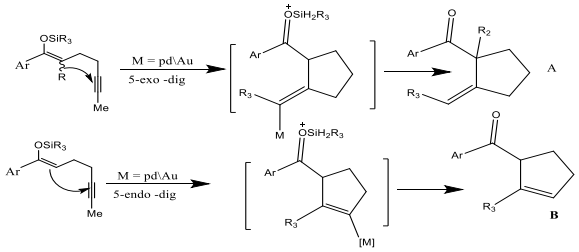


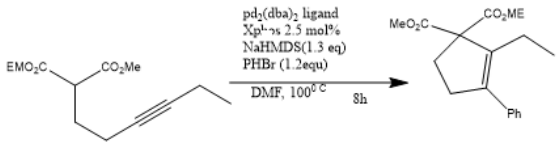
Figure: 9

3.0 Au and Pd catalysed reaction

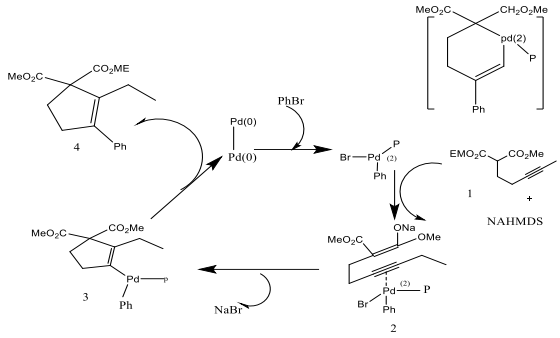
In 2010, Mambo et al. developed methods for cycloisomerisation of simple keto-alkynes which take place at room temperature under mild conditions using gold catalysts [22,23]. In this reaction, the catalyst used is n[$Ph_3PAuCl/AgOTf$ (6 mol%) and CH_2Cl_2 (0.1 M)] which is kept for 3.5 hours at room temperature. The yield is 77%. Electron withdrawing groups like -COOEt and -CN give a good yield of the exo-cyclised product [24]. In 2012, Jean-Francois Brazeau et al. discovered a complementary method for enantioselective transition metal-catalysed cyclisation with silyioxyenynes using chiral phosphine ligands. With Pd catalyst, 1,6-silyloxyenynes form 5-membered endo ring while use of Au catalyst and 1,5 and 1,6-silyloxyenynes give 5- membered exo- ring. Both show high ee% with a cyclopentanoid structure [25] **(Scheme 10)**. According to Daishi et al, 5- endo dig cyclised ring is unexplored despite their synthetic utility [26–30]. Detailed investigations [31,32] recently revealed unfavorable stereoelectronic effects operating on 5-endo-dig cyclisation but Baldwing rule assigned 5-endo as the favorable process [33]. The cyclisation mode was again restricted to exo [34,35]. In this reaction ligand selectivity X-PhOS show the best yield 95%, bulky electronic groups do not retard the 5-endo dig cyclisation. Aryl halides give a good result without affecting other functional group[36] **(Scheme 11 & 12)**.



Scheme: 10



Scheme: 11

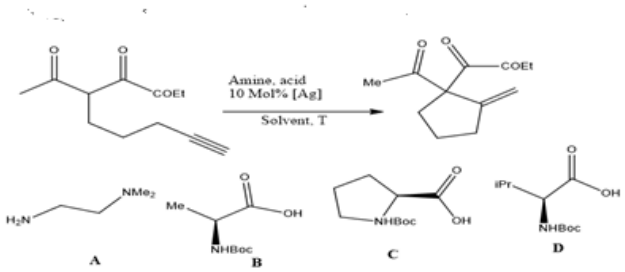


Scheme: 12 Possible reaction mechanism

In 2019, R. D. Reeves et al. showed a 5-membered carbocyclic framework using Pd as a catalyst with allene which favoured a syn relationship between C-1 and C-5. Gem dial substitutions in such reactions give good yields. With Au catalyst, 5-Endo attack takes place at the Y carbon which shows anti-relationship between R_1 at C-5 and cis at C-1. The strain is more in the carbopalladation step [37]

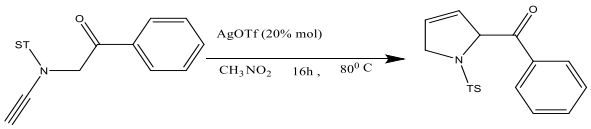
4.0 Ag catalysed reaction

A silver salt is mainly used as a cocatalyst with gold such as $AgBF_4$, $AgSbF_6$, and $AgPF_6$ as they are very hygroscopic and difficult to handle. AgNT on the other hand is more stable. This reagent proves to be an efficient catalyst for nucleophilic addition to the alkyne [38]. It is also good for the cyclo isomerisation of silylalkynyl enol ether. DCE and toluene enhances the yield. DCE prefers the formation of exo- regioisomer, while toluene shows endo cyclisation. Exo product is dominant in this article, and a large ring substrate can make six-member endo-dig cyclisation. Schafer et al. used AgNT (5 mol %) and solvent DCE at 20 ^{0}C for 14 hours to give 88% product yield. Iodo trapping provides a valuable synthon in organic chemistry [39]**.** In 2013, Hack et al. developed a novel catalytic system for the amine-silver co-catalysed Conia-ene reaction. This group used AgNT and amine with chloroform as a solvent to give a good yield, 89%. With different amines or amino acids, the yield may vary **(Table 1)**. An increase in the catalyst amount has a negative effect on product formation. Protic solvents increase the yield, with 90% ee and 76% yield at room temperature. In 2013, Boominathan et al. developed a novel method for synthesising 3-pyrrolines via 5-endo-dig carbocyclization. They used AgOTF 20 mol 5% catalyst and CH3NO2 as solvent at 80 ^{0}C **(Scheme13).** This reaction tolerates both electron-withdrawing groups as well as electron-donating groups [40] **.**

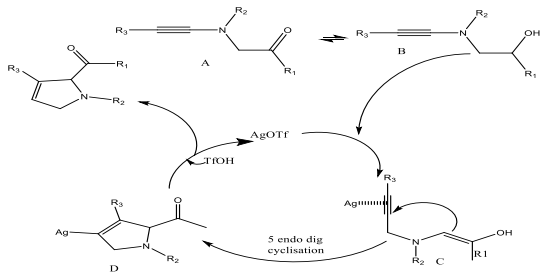


Entry	[Ag]	A [Mol%]	Acid (mol%)	Solvent	Yield[%]
1	$AgNTf_2$	20	TFA(20)	$CHCl_3$	84
2	$AgNTf_2$	20	B(20)	$CHCl_3$	86
3	$AgNTf_2$	20	C(20)	$CHCl_3$	86
4	$AgNTf_2$	20	D(20)	$CHCl_3$	86
5	$AgNTf_2$	10	B(10)	$CHCl_3$	89

Table: 1 Optimisation of amine silver co-catalysed Conia-ene reaction

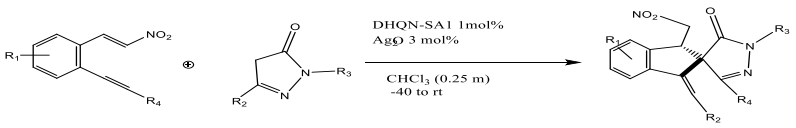


Scheme: 13



Scheme: 14 Possible mechanisms of AgOTf

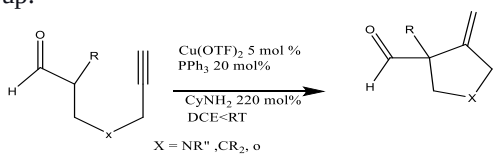
In 2016, Hack et al. combined transition metal and organocatalysis for the asymmetric synthesis of annulated heterocyclic compound [41]**.** Ag combined more easily with organo-catalyst as compared to others. In the one-pot synthesis of 5 membered 4-spiropyrazolons, most of the organocatalysts generated 6-membered spiro derivatives [42]**.** Lu et al. made [4+1] annulation using pyrazolones and allenoate. In this article, for the cyclization, reaction conditions are requiring a temperature of - 40^{o} C with use of 1% mole DHQN-SA1 and, 3% AgO_2 **(Scheme 15)**. In substrates that contain a phenyl ring, the reaction can also take place without the metal, but proceeds slowly [2].



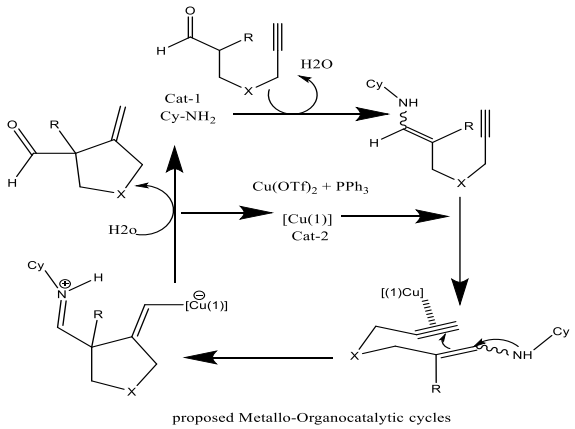
Scheme: 15

5.0 Cu catalysed reactions

To overcome the limitation of low acidity and low enolisable ability, in 2010, Montel et al. used Cu as a catalyst for Conia-ene reactions. This group used Cu[(phen)$(PP)_2$] in solvent dioxane 20 mol% at 150^{o}C in the microwave to form the 5-exo cyclic compound. This condition can only be applied to less reactive diesters[43]**.** Recent studies show a strong influence of amine as co-catalysts over the reaction pathway. In 2012, Montaignac et al reported Copper (1)-amine metal-organocatalysis synthesis of carbo- and heterocyclic compound. Cyclohexanamine was selected as the best catalyst because it quickly generates the enamine intermediately from disubstituted aldehydes. In this case, this group used five mol% $Cu(OTf)_2$, 20 mol% triphenylphosphine and 20 mol% of cyclohexylamine in DCE at rt [44] **(Scheme 16)**. Gem-dimethoxy methyl like compounds gives good yield. Phenyl substrates show promising results, but they show a slow reaction. In 2015, Zhu et al. used Cu as a catalyst for synthesising the heterocyclic compound without using base [45]**.** In 2016, one of the studies reported the effect of microwave on catalytic enantioselective Conia-ene reaction. In this reaction, five mol% Cu (OTf)$_2$ is used as a catalyst with 20 mol% chiral amines in the presence of solvent DCE. The study shows an increase in the kinetic rate by 1.15 times, compared to conventional heating methods, where the product is formed without affecting enantioselectivity [46]. Azaspiro compounds are increasingly being used in drug discovery due to their 3-dimensional structure [47]. In 2017, Frederic Beltran et al. developed a method for direct spirocyclization from keto-sulfonamide using CuSO4·5H2O, 1,10-phenanthroline and CaCO3 as a base. The reaction gave a good yield if the substrate has an electron-withdrawing group.[48]



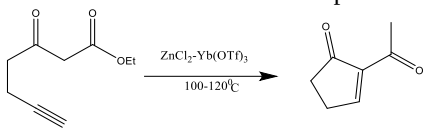
Scheme :16



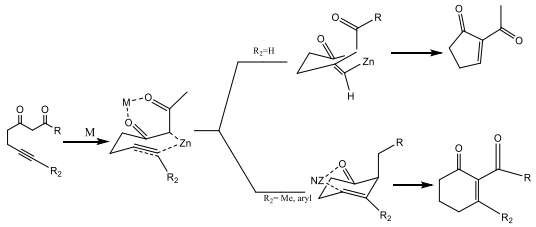
Scheme: 17

6.0 Zn catalysed reactions

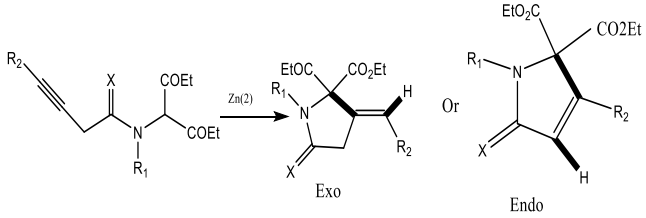
Before 2010, most of the catalysts reported were either expensive or used a harmful solvent. Most of the work done was reported on alpha - alkynic beta-keto ester. Only two papers reported work on linear β-ketoester substrates [49,50]. This group used Zn, which is not as expensive as compared to others. After many trials, they found that zinc (II) chloride combined with ytterbium (III) to show good product formation. Terminal alkyne substrate shows a good yield of the 5-membered exo- product while internal alkyne shows endo product in a six-member ring. Electron donating group show more yield than the electron-deficient substrate[51] **(Schemes 18, 19)**. In 2011, Wilfried and Burton used $ZnCl_2$ for the catalytic system alkynyl-aminomalonates, applicable to five-endo dig cyclisation. Hence it is also a handy method for the synthesis of heterocyclic compounds. When -CO2Me, -CO2Bn, -Bn and internal alkyne are used, then endo product is formed with excellent yield. If the reaction is carried out with ZnI, then also excellent yield is reported. However, the reaction takes place slowly[52] **(Schemes 20, 21)**. In the above two articles with Zn catalysts, not much is mentioned about the stereochemistry of the product. In 2012, Suzuki et al. made a four-component catalyst system for the 5-endo-dig cyclisation of β-ketoester with an internal alkyne. Before this, only one paper showed Endo cyclisation, but they could not get good ee %. In this case, they got a good yield and ee% and also an unequal spirocenter. The four components used are Zn (OAc)2/Yb(OTf)3/Box-Ph/HFIP, and it uses solvent DCE at low temperature[53] **(Scheme: 22)**.



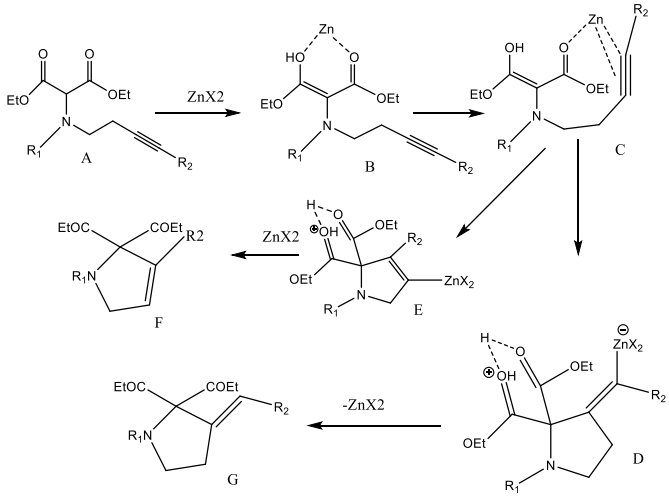
Scheme: 18



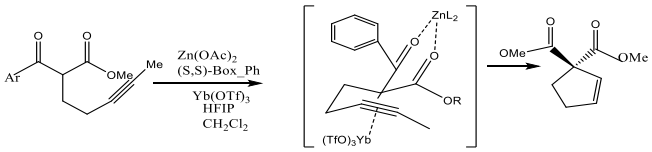
Scheme: 19



Scheme: 20



Scheme: 21 Possible reaction mechanism



Scheme: 22

II. CONCLUSION

Conia-ene reactions using transition metals enhanced productivity even under mild conditions. It is a very handy method for synthesis of heterocyclic compound, carbocyclics, etc, and it has often been put to use in the synthesis of the core skeleton of many natural products through a combination of other metals and organocatalysts. The utility and scope of the reaction thus

increases to a large extent. However, its true scope can be put to explore only when a substantial amount of work is done in understanding the reaction mechanisms.

III. ACKNOWLEDGEMENT

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