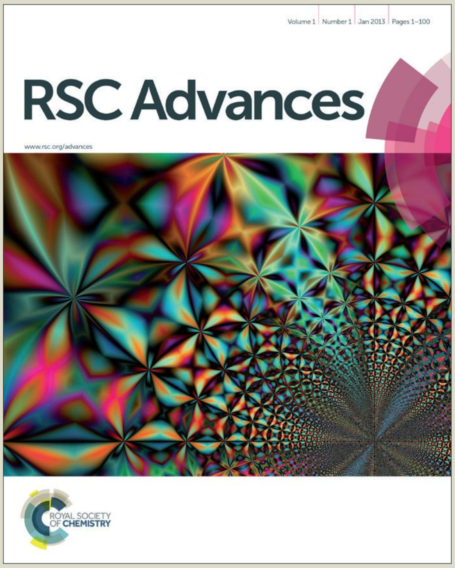
RSC Advances



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

ARTICLE

Facile synthesis of $ZnAl_2O_4$ nanoparticles: Efficient and reusable porous nano $ZnAl_2O_4$ and Copper supported on $ZnAl_2O_4$ catalysts for one pot green synthesis of propargylamines and imidazo[1,2-a]pyridines by A^3 coupling reactions

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Triveni Rajashekhar Mandlimath and Kulathu I. Sathiyanarayanan*

A simple, facile and efficient route was developed for the synthesis of nano $ZnAl_2O_4$ using ethanolamine. $ZnAl_2O_4$ nanoparticles were found to be smaller when calcined at 500 °C than at 700 °C. The synthesized nano $ZnAl_2O_4$ exhibited a high surface area of 147 m^2/g with pore volume 0.2 cm^3/g. $ZnAl_2O_4$ nanoparticles were found to be spherical in shape with size ranging from 3 - 7 nm. For the first time, we explored the catalytic activity of nano $ZnAl_2O_4$ for the synthesis of propargylamines by A^3 coupling of aromatic aldehydes, piperidine and phenyl acetylene. High yields were achieved without any side product. We developed Cu/ nano $ZnAl_2O_4$ and utilized it for imidazo[1,2-a]pyridines synthesis by three component coupling of aromatic aldehydes, 2-aminopyridine and phenylacetylene under N_2 atmosphere. We achieved good yields, and both nano $ZnAl_2O_4$ and Cu/ nano $ZnAl_2O_4$ were recycled for five times successfully. Both the protocols were simple, one pot, solvent-free, economical and involved no additive. They could be an alternative to the existing protocols which involve homogeneous and expensive noble metal catalysts for these reactions.

INTRODUCTION

Multicomponent coupling reactions (MCRs) are the potential tool to synthesize diverse complex organic scaffolds from simple organic moieties via one-pot process. These MCRs have gained extensive interest of researchers because of their uniqueness in yielding high atom economy and often high selectivity. In recent times, intense investigation for the development of eco-friendly solvent free MCRs have been a great concern in order to reduce environmental pollution caused by hazardous organic solvents. Among the MCRs, A^3 coupling of (i) aldehyde, alkyne, and amine and (ii) aldehyde, alkyne, and 2-aminopyridine *via* activation of a terminal alkyne C-H bond have been great importance in recent years. The resulting propargylamines and imidazo[1,2-a]pyridines are nitrogen containing compounds with diverse applications: Propargylamines are the important key components of various natural products,[1] versatile precursors for the synthesis of quinolines,[2a] indolizines,[2b]oxazoles,[2c] pyrroles,[2d] and pyrrolidines,[2e] and also potential building blocks for the synthesis of the therapeutic drug molecules such as isosteres,[3a] allylamines,[3b] β-lactams,[3c] conformationally restricted peptides, and oxotremorine analogs.[3d] Recently propargylamine derivatives have attracted attention due to their excellent pharmacological activity. They are strong neuroprotective[4a, 4b] and anti-apoptotic agents[4c]. Propargylamine derivative rasagiline is used for treating early Parkinson's disease[5]. Whereas, imidazo[1,2-a]pyridines are the versatile scaffolds mainly occurred in wide range of bioactive molecules and also known for their antiviral,[6a] anti-inflammatory,[6b,6c] analgesic,[6c] antipyretic,[6c] antiulcer[6d] and antibacterial properties.[6e] Commercial drugs such as Alpidem

---

[a] Address here.
[b] Address here.
[c] Address here.
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

(anxiolytic agent),[7a] Zolpidem (insomnia),[7b]Olprinone (for the treatment of acute Heart failure),[7c] and Minodronic acid (for the treatment ofosteoporosis)[7d] contain imidazo[1,2-a]pyridine moiety. In addition to the above applications, imidazo[1,2-a]pyridine derivatives have incurred significant importance as central ligands in the field of electronic devices.[8]

Conventional method of synthesizing propargylamines requires the generation of metallated alkynes utilizing various strong bases such as alkoxides[9a], hydroxide,[9b] $LiAlH_4$,[9c] butyl lithium[9d,9e], LDA[9e] and Grignard reagents[9f] and attack of the generated metallated alkynes to imines. The major drawbacks of this protocol are the need of highly moisture-sensitive reagents in stoichiometric quantity and harsh reaction conditions. In recent years, A^3 coupling of aldehydes, amines and alkynes via C-H activation have been developed as alternative to the traditional method, wherein water is the only byproduct. Variety of homogeneous catalysts like $Zn(OAc)_2$,[10a] AgI,[10b] AuCl,[10c] AuI,[10c] $AuCl_3$,[10c] $AuBr_3$,[10c] $FeCl_3$,[10d] CdI_2,[10e] $InCl_3$,[10f] $InBr_3$,[10g] CuCl,[10h] CuBr,[10h] CuI,[10h] $NiCl_2$,[10i] Hg_2Cl_2,[10j] Au(III) complexes,[11] Ag(I) complexes[12] have been applied. Theses catalysts mostly require hazardous solvents like acetonitrile, toluene, and tedious workup process and often need inert atmosphere. In order to replace the homogeneous catalysts, in recent years, heterogeneous catalysts have been employed: Au nanoparticles,[13a] Ag nanoparticles,[13b] Au/CeO_2,[14] Au/ZrO_2,[14] Au nanoparticles stabilized on montmorillonite,[15] Au and Ag nanoparticles on Egg shell,[16] Ag immobilized on ZnO nanoparticles,[17]nanocrystallineMgO stabilized Au nanoparticles,[18] polystyrene supported NHC-Ag(I) catalyst,[19] Au nanoparticles on Al_2O_3,[20] Cu nanoparticles stabilized on modified montmorillonite.[21] Although these are heterogeneous in nature, they are expensive and often require toxic toluene, THF solvents, prolonged duration to achieve good yields and metals often lost during the reaction. Ionic liquids immobilized catalysts containing imidazolium molecule with BF_4 or PF_6 anions have been reported[22]. These catalysts have serious limitation due to their high cost and disposable problem as they are highly toxic. Metal oxides such as Cu/SiO_2,[23] Cu-Zeolite,[24] Zinc titanate nanopowder[25] and Co_3O_4[26] and copper aluminium based nanocomposites[27] have been investigated for propargylamines synthesis. However, most of the catalysts need organic solvent and require long time to achieve high yields.

Various protocols are available in the literature for the synthesis of imidazo[1,2-a]pyridines using Cu-MOF,[28] $Cu(OTf)_2$,[29] CuCl,[29] $InBr_3/Et_3N$,[30] $CuSO_4$-glucose,[31] Iodine,[32]$CuI/NaHSO_4$-SiO_2,[33] $CuSO_4$/TSOH,[34] $ZnCl_2/CuCl$[35] as catalysts. These protocols suffer from serious issues such as need of homogeneous catalysts, long duration and often require additives (like glucose, TsOH and Et_3N) along with metal catalysts.

Considering the biological and therapeutic importance of propargylamines and imidazo[1,2-a]pyridines, and also the inefficiency of existing protocols for their synthesis, in continuation of our previous reports,[36, 37] herein, we developed a facile synthetic method for nano porous $ZnAl_2O_4$ with large surface area and employed it as an efficient catalyst for the synthesis of propargylamines. Cu nanoparticles supported on the synthesized nano $ZnAl_2O_4$ were efficiently used as catalyst for imidazo[1,2-a]pyridines. To the best of our knowledge, this is the first report for nano $ZnAl_2O_4$ synthesis using ethanolamine and protocols for the one pot synthesis of propargylamines and imidazo[1,2-a]pyridines using nano $ZnAl_2O_4$ and Cu/nano $ZnAl_2O_4$respectively. The synthetic route of nano $ZnAl_2O_4$ was very simple. Being solvent free, environmentally friendly, the protocols for A^3 coupling reactions utilize low cost reusable catalysts.

Results and discussion

Powder XRD and BET analysis

Figures 1a and 1b display powder XRD patterns of $ZnAl_2O_4$ calcined at 500 °C (ZAO5) and $ZnAl_2O_4$ calcined at 700 °C (ZAO7) respectively. Both materials were phase pureand crystallized in face centered cubic phase. All the peaks were indexed based on the standard ICDD data (# 821043). XRD peak broadening of ZAO7 was found to be lesser than that of ZAO5. This indicates the crystallite size of nano $ZnAl_2O_4$ increased with increase in calcination temperature. The average crystallite size of ZAO5 and ZAO7 determined from Scherrer's formula was 5 nm and 7 nm respectively.XRD pattern (Fig. 2) of Cu/ZAO5 affirmed the presence of copper diffraction peaks (2θ = 43.31 and 50.44) along with$ZnAl_2O_4$ peaks. No other metal oxide peaks were observed in XRD. From the BET method, the specific surface area and pore volume of ZAO5 and ZAO7 were found to be 147 m^2/g, 0.2 cm^3/g and 100 m^2/g, 0.14 cm^3/grespectively. This evidenced decrease in the surface area and pore volume of $ZnAl_2O_4$ upon increasing the calcination temperature from 500 °C to 700 °C.

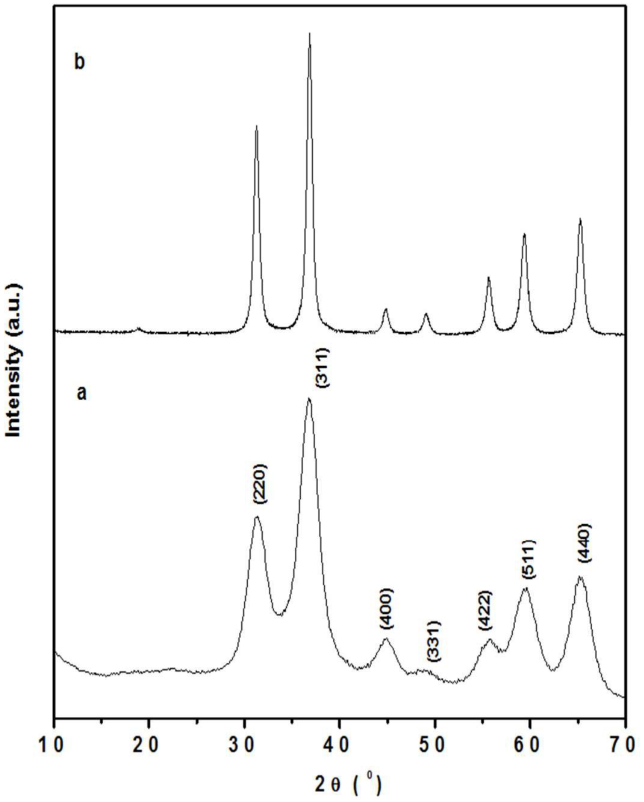


Fig. 1 Powder X-ray diffraction patterns of (a) ZAO5 and (b) ZAO7

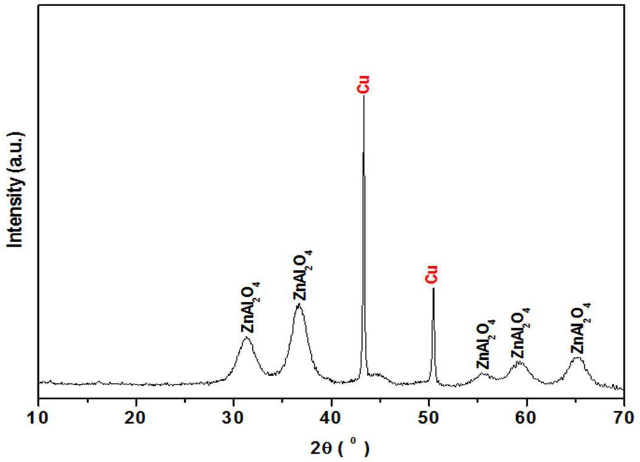


Fig. 2 Powder X-ray diffraction pattern of Cu/ZAO5

In the present work, ethanolamine acted as complexing as well as precipitating agent. The gradual addition of ethanolamine led to the formation of the complex with zinc nitrate and aluminium nitrate, which upon calcinations resulted in nanosized particles of $ZnAl_2O_4$. The evolution of NH_3 and CO_2 gases during calcinations left the pores in the catalysts.In our previous report[36], we synthesized $ZnAl_2O_4$ in the absence of ethanolamine. From the micrographs and powder X-ray analysis, it was identified that the particles were in the range of 5 µm. Hence, these observations indicated the presence of ethanolamine controlled the $ZnAl_2O_4$ particle size.

In the case of $Cu/ZnAl_2O_4$, surface area was found to be 50 m^2/g with pore volume 0.07 cm^3/g. This confirmed the occupancy of copper over the surface and pores of nano $ZnAl_2O_4$.

Microscopic and TPD analysis

SEM images of ZAO5 (Fig. 3a) and Cu/ZAO5 (Fig. 3b) showed aggregation of the particles. EDX spectra (supplementary data) affirmed the presence of Zn, Al, O and Zn, Al, Cu and O elements in the catalysts ZAO5 and Cu/ZAO5 respectively. The atomic percentage matched with the theoretical values. EDX spectra of ZAO5 and Cu/ZAO5 showed the absence of C and N peaks,which indicates the absence of ethanolamine.

TEM images of ZAO5 and Cu/ZAO5are shown in Fig. 4a and 4b.The particles were spherical in shape. Crystalline nature and homogeneous distribution of ZAO5 particles were evident from Selected Area Electron Diffraction (SAED) Pattern (Fig. 4a inset). Presence of copper nanoparticles on ZAO5 was identified by TEM-EDX analysis (Supplementary data). Crystalline nature of the Cu/ZAO5 particles was seen from Selected Area Electron Diffraction (SAED) Pattern (Fig. 4b inset). The obtained histogram revealed the narrow size distribution of ZAO5 nanoparticles with 3-7 nm size (Fig. 5).

NH_3-TPD pattern (Fig. 6a) shows two peaks at 194 ºC and 367 ºC. The ZAO5 possessed medium acidic sites. The total acidity was 5 mmol py/g. CO_2 - TPD pattern (Fig. 6b) exhibited three peaks at 154 ºC, 334 ºC and 438 ºC. The peak at 154 ºC was associated with weak basic site (surface hydroxyl group). The peaks at 334 ºC and 438 ºC were associated with medium (due to M^{n+}-O^{2-}pair) and strong (due to isolated O^{2-}) basic sites on the catalyst's surface respectively.[38] The total basicity of the catalyst was found to be 2.5 mmol CO_2/g.

XPS analysis was carried out for the sample Cu/ZAO5 to know the oxidation state of copper. Fig. 7 shows the XPS spectrum of

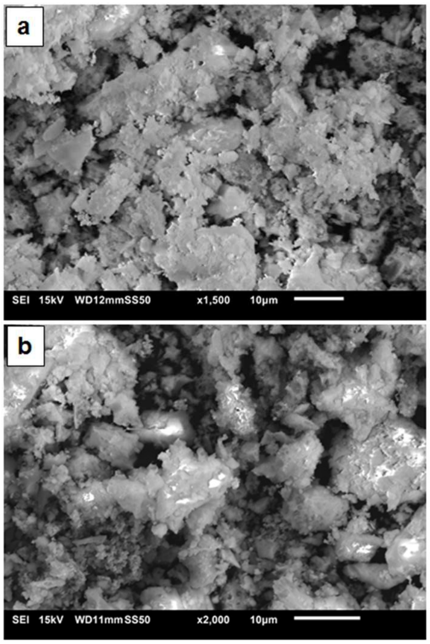


Fig. 3 SEM images of (a) ZAO5 and (b) Cu/ZAO5

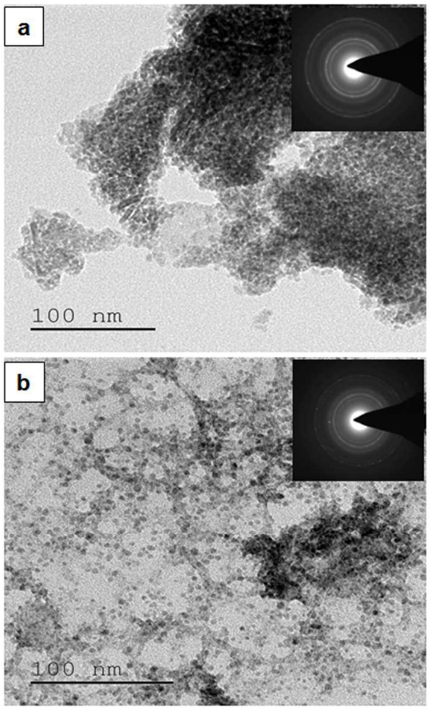


Fig. 4 TEM images of (a) ZAO5 and (b) Cu/ZAO5; Inset show respective electron diffraction patterns

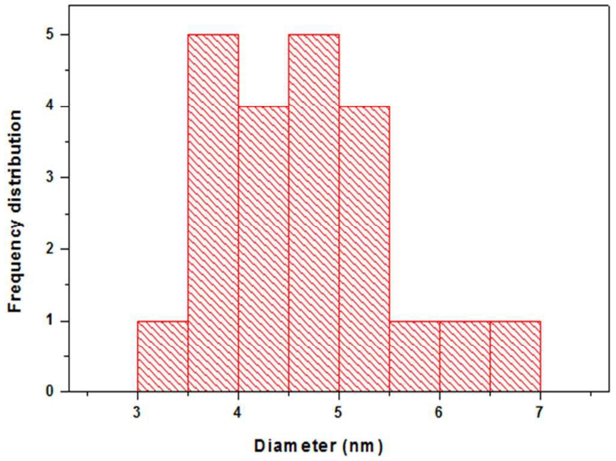


Fig. 5 Histogram of ZAO5

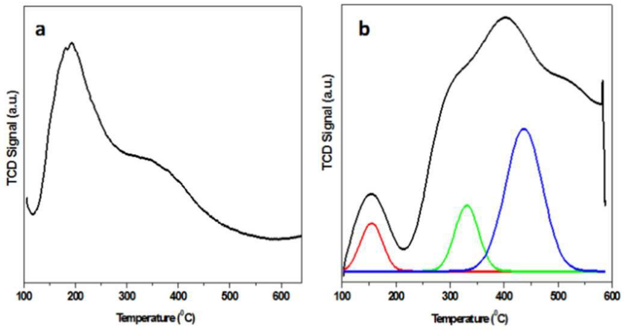


Fig. 6 NH_3-TPD (a) and CO_2-TPD of ZAO5

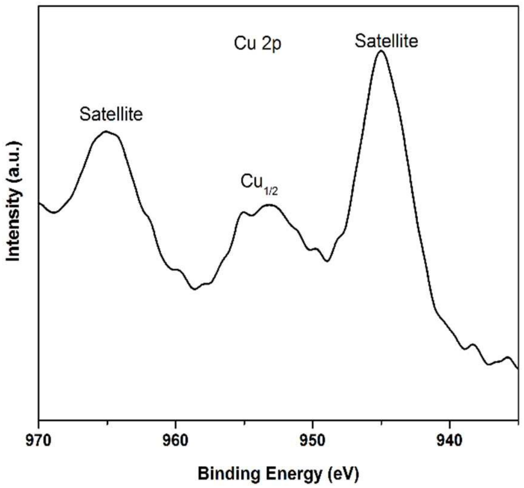


Fig. 7 XPS spectrum of Cu/ZAO5

Cu/ZAO5. The peaks appeared at 943 eV and 962 eV, characteristic satellite peaks, belong to Cu^{2+}. The peakappeared at 953 eV associated with Cu $2p_{1/2}$.[39]Thisconfirmed that the copper underwent surface oxidation and that the copper surface was in the form of CuO.

Catalytic role of nano $ZnAl_2O_4$ and Cu/nano $ZnAl_2O_4$ for A^3 coupling reactions

Initially we investigated the catalytic activity of commercial ZnO, Al_2O_3, bulk $ZnAl_2O_4$and synthesized nano $ZnAl_2O_4$ for the propargylamine synthesis by refluxing benzaldehyde (3 mmol), piperidine (3.3 mmol) and phenylacetylene (3.6 mmol) in toluene at 90 °C for 6 h. We found that nano $ZnAl_2O_4$ gave better yield compared to other catalysts (Table 1).

Due to the smaller surface area and lesser number of active sites, bulk $ZnAl_2O_4$ showed poor yield. In order to optimize the solvent system for the propargylamine synthesis using nano $ZnAl_2O_4$, the reaction was carried out in various solvents including water. It was found to end up with moderate yields. We observed that under neat conditionsnano $ZnAl_2O_4$ resulted in 99.9% yield of propargylamine (Table 2) (Scheme 1).

Table 1. Screening of the catalysts for one-pot synthesis of propargylamines

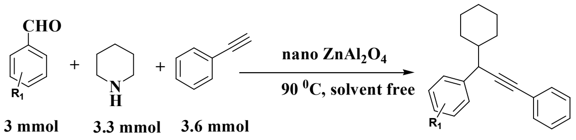
Entry	Catalyst	Reaction time (h)	% Yield [(a)]
1	ZnO	6	50
2	Al_2O_3	6	45
3	Bulk $ZnAl_2O_4$	6	60
4	Nano $ZnAl_2O_4$	6	82

Reaction conditions: Reactants: benzaldehyde (3 mmol), piperidine (3.3 mmol) and phenylacetylene (3.6 mmol); solvent: 5 ml toluene, temperature: 90 °C, [a] GC

Table 2. Effect of solvents on the synthesis of propargylamines

Sl. No.	Solvent (5 ml)	Reaction time (h) /Yield (%)[a]
1	Toluene	4/82
2	Ethanol	4/61
3	Tetrahyrofuran	4/50
4	Methanol	4/62
5	Acetonitrile	4/51
6	-	4/99.9

Reaction conditions: Reactants: benzaldehyde (3 mmol), piperidine (3.3 mmol) and phenylacetylene (3.6 mmol), temperature: 90 °C, [a] GC



Scheme 1. Nano $ZnAl_2O_4$catalyzed synthesis of propargylamine derivatives under solvent free conditions

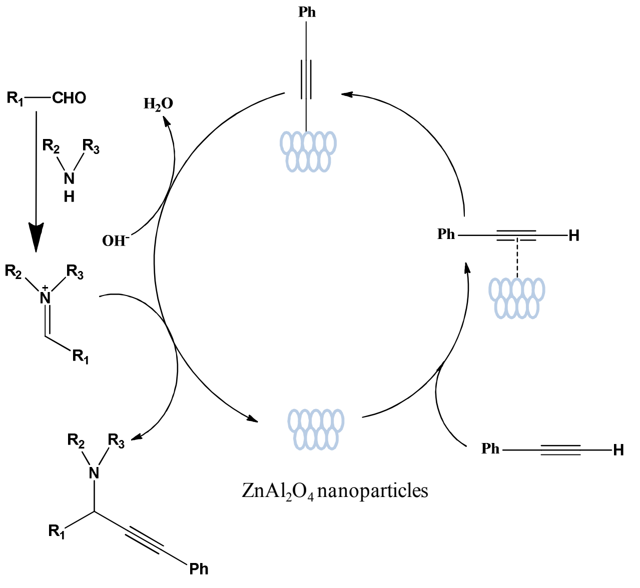
This evidenced the efficiency of nano $ZnAl_2O_4$ under solvent free condition. Further, we explored the catalytic activity of nano $ZnAl_2O_4$ for various benzaldehyde derivatives in order to understand the generality of the catalysts. We found 98-99.9% yield (Table 3).

The plausible mechanism for propargylamine synthesis using nano $ZnAl_2O_4$ (Scheme 2)was proposed based on the literature reports. Iminium ion was formed from aldehyde and piperidine at room temperature in the initial step. Due to the presence of acidic and basic sites, catalyst nano $ZnAl_2O_4$ involved in the activation of the C–H bond of acetylene forming $ZnAl_2O_4$–acetylide intermediate in the second step. In the final step, iminium ion reacted with $ZnAl_2O_4$–acetylide intermediate and resulted propargylamine.

Table 3. One-pot synthesis of propargylamine derivativesusing nano $ZnAl_2O_4$

Sl. No.	R_1	Reaction time (h)/yield$^{(a)}$
1	H	4/ 99.9
2	4 - CH_3	4/ 99
3	4 - OCH_3	4/ 99
4	4 - Cl	4/ 99.9
5	4 - F	4/ 99
6	2 - F	4.5/ 98
7	2 - MeO	4.5/ 98
8	2, 4 - Cl	5/ 98
9	3,4 - OCH_3	5/98

Reactants: benzaldehyde (3 mmol), piperidine (3.3 mmol) and phenylacetylene (3.6 mmol), solvent free, temperature: 90 °C, ^{a}GC



Scheme 2. Plausible mechanism for propargylamine synthesis using nano $ZnAl_2O_4$ under solvent free conditions

In order to reuse the catalyst, after every cycle the catalyst was recovered by filtration using whatman filter paper, washed with acetone to remove organic moieties and dried at 100 °C. We recycled the catalyst for 5 cycles without significant loss of activity (Fig. 8). Powder XRD pattern of nano $ZnAl_2O_4$, before and after reusability appeared to be the same indicating the re-existence ofcatalyst without any change (Fig. 9a and 9b).

We compared the activity of nano $ZnAl_2O_4$ with reported catalysts for propargylamines synthesis (Table 4) and understood that most of the reported catalysts are expensive, require solvent and inert atmosphere and also need prolonged reaction time. Nano $ZnAl_2O_4$ yielded high yield of propargylamine in lesser reaction time under solvent free condition.

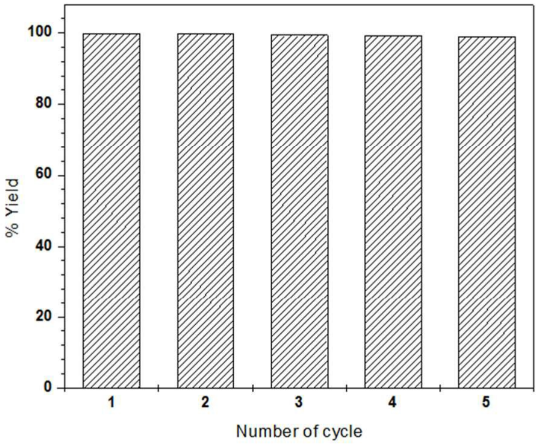


Fig. 8 Reusability of ZAO5 for the synthesis of propargylamie

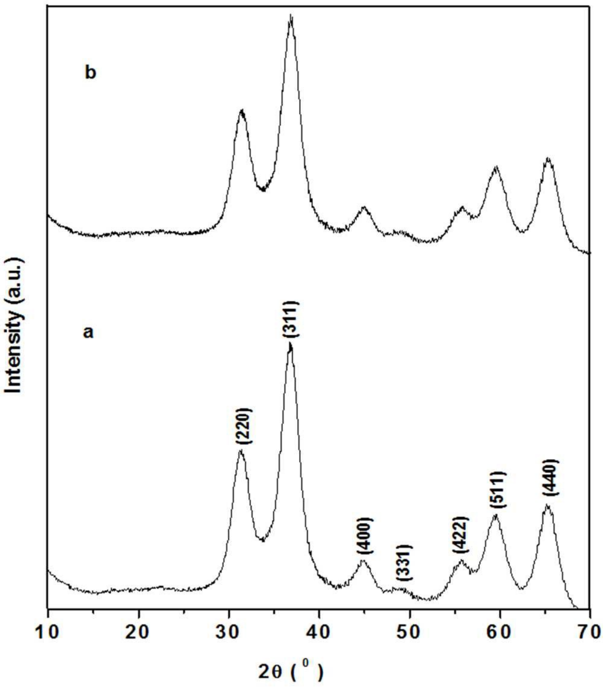


Fig. 9 Powder X-ray diffraction patterns of (a) fresh ZAO5 and (b) reused ZAO5

To understand the scope of the synthesized catalyst nano $ZnAl_2O_4$ for three component coupling reaction, we tested the catalytic activity of nano $ZnAl_2O_4$ for the coupling reaction between benzaldehyde, 2-aminopyridine and phenylacetylene. But unfortunately no reaction took place (Table 5).

Table 4. Comparison of the activity of the $ZnAl_2O_4$ with other catalysts for the synthesis of propargylamines

Sl. No.	Catalyst	Solvent	Temperature/ reaction condition	Reaction time	Yield (%)	Reference
1	$NiCl_2$	Toluene	110 °C/Argon	8 h	95	10 (i)
2	CuI	PEG	100 °C/Nitrogen	12 h	87	10 (h)
3	SiO_2@Cu	Toluene	110 °C	5 h	94	23
4	$InCl_3$	Toluene	120 °C/Argon	20 h	90	10 (f)
5	*NAP-Mg-Au(0)	Toluene	100 °C	15 h	98	18
6	Nano Co_3O_4	Toluene	130 °C	15 h	87	26
7	Nano $ZnAl_2O_4$	-	90 °C	4 h	99.9	present work
	* Nano Active Magnesium Oxide Plus					

Reactants: benzaldehyde piperidine, phenylacetylene

Table 5 Comparison of the activity of the catalysts for imidazo[1,2-a]pyridine

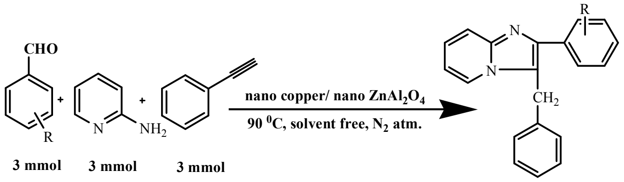
Sl. No.	catalyst	Yield (%)a
1	$ZnAl_2O_4$	nil
2	CuO	61
3	Cu powder	69
4	8 wt% Cu/ nano $ZnAl_2O_4$	90
5	8 wt% Ni/ nano $ZnAl_2O_4$	51
6	8% Cu-Ni/ nano $ZnAl_2O_4$	55

Reactants: benzaldehyde (3 mmol), 2-aminopyridine (3 mmol) and phenylacetylene (3 mmol), solvent free, N_2 atmosphere, temperature: 90 °C, ^{a}GC

Understanding the need of copper and other transition metal catalysts for this reaction, we explored the catalytic activity of various catalysts such as CuO, Cu powder, 8 wt% Cu/ nano $ZnAl_2O_4$, 8 wt% Ni/ nano $ZnAl_2O_4$ and 8% Cu-Ni/ nano $ZnAl_2O_4$ under solvent-free condition as well as with solvent. The catalysts Ni/nano $ZnAl_2O_4$ and Cu-Ni/ nano $ZnAl_2O_4$ resulted in moderate yields, whereas, 8 wt% Cu/ nano $ZnAl_2O_4$ resulted in better yields under solvent-free and in the presence of N_2 atmosphere (Scheme 3). Hence, it was evident that the active site for imidazo[1,2-a]pyridine synthesis was copper and that nano $ZnAl_2O_4$ acted as support for copper nanoparticles because it provided large surface area and also aggregation of the copper nanoparticles was reduced. We carried out the reaction for other benzaldehyde derivative and 94-89% yields were achieved in 4-6h(Table 6).

Reusability of the catalyst was performed for the coupling between benzaldehyde, 2-aminopyridine and phenylacetylene by recovering the catalyst after every cycle. This was followed by washing with acetone and drying under vacuum. After every cycle, leaching of the metal ion was tested by AAS, and was found to be nil. We successfully recycled the catalyst five times without change in its activity (Fig. 10) and the catalyst was recovered without any change (Figs. 11a and 11b).

The plausible mechanism for imidazo[1,2-a]pyridines synthesis using nano $ZnAl_2O_4$ (Scheme 4)was proposed on the basis of literature reports. In the initial stage, imine was formed by the condensation of 2-aminopyridine with aldehydes. Formation of propargylamine occurred due to the nucleophilic attack of alkyne to imine. Due to the C-H activation of alkyl triple bond by copper on $ZnAl_2O_4$,intramolecularnucleophilic attack of nitrogen in pyridine ring to the triple bond either in 5-exo-dig (C-a attack) or 6-endo-dig way (C-b attack) took place. Which was later followed by aromatic isomerization of the cyclic intermediate led to imidazo[1,2-a]pyridines.



Scheme 3 Cu/nano $ZnAl_2O_4$catalyzed synthesis of imidazo[1,2-a]pyridine derivatives under solvent free condition

Table 6. One-pot synthesis of imidazo[1,2-a]pyridine derivatives

Sl. No.	R_1	Reaction time (h)/yield$^{(a)}$
1	H	6/ 90
2	4 - CH_3	4/ 89
3	4 - OCH_3	4/ 89
4	4 - Cl	4/ 94
5	4 - F	4/ 94
6	2 - F	4.3/ 90

Reactants: Aldehyde (3 mmol), 2-aminopyridine (3 mmol) and phenylacetylene (3 mmol), solvent free, N_2 atmosphere, temperature: 90 °C, ^{a}GC

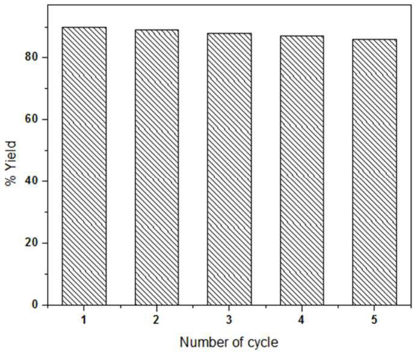


Fig. 10 Reusability of ZAO5 for the synthesis of imidazo[1,2-a]pyridines

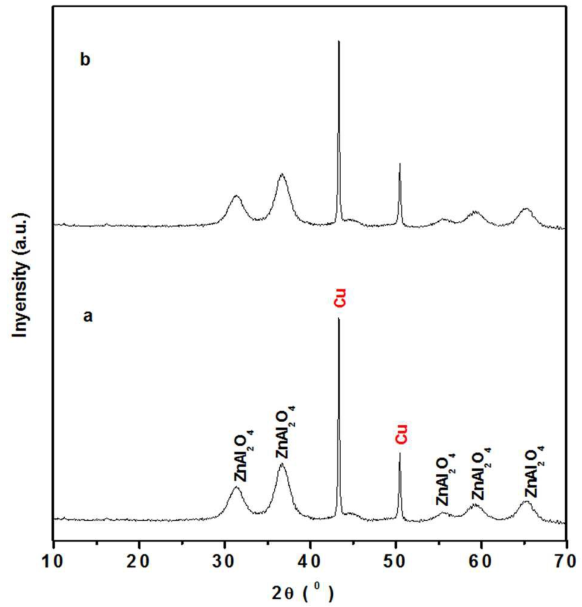
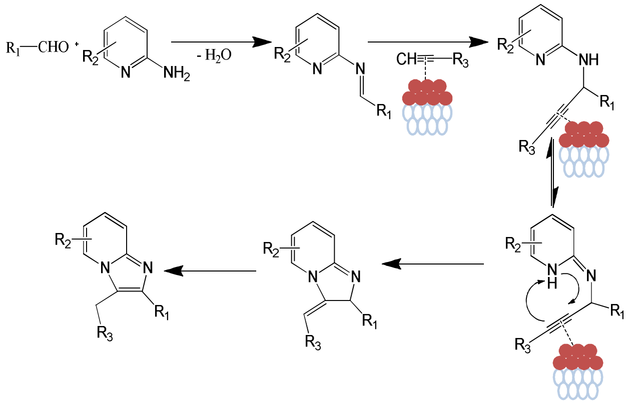


Fig. 11 Powder X-ray diffraction patterns of (a) fresh Cu/ZAO5 and (b) reused Cu/ZAO5



Scheme 4. Plausible mechanism for the synthesis of imidazo[1,2-a]pyridine using Cu/nano $ZnAl_2O_4$ under solvent free conditions

We compared the activity of Cu/nano $ZnAl_2O_4$ with reported catalysts for imidazo[1,2-a]pyridinessynthesis (Table 7). Most of the reported catalysts are expensive, require additive and need prolonged reaction time. Cu/ nano $ZnAl_2O_4$ provided good yield of imidazo[1,2-a]pyridinesin lesser reaction time under solvent free condition.

Table 7. Comparison of the activity of the Cu/ZnAl2O4 with other catalysts for the synthesis of propargylamines

Sl. No.	Catalyst	Solvent	Temperature/reaction condition	Reaction time	Yield (%)	Reference
1	CuCl + Cu(OTf)$_2$	Toluene	120°C/ Nitrogen	16 h	93	28
2	InBr3	Toluene	Reflux/ Et$_3$N	12 h	82	30
3	Iodine	Water	60 °C	6 h	85	32
4	CuSO$_4$/ TSOH	Toluene	110 °C	18 h	60	34
5	Cu/nano ZnAl$_2$O$_4$	-	90 °C	6 h	90	Present work

Reactants: Benzaldehyde, 2-aminopyridine and phenylacetylene

EXPERIMENTAL

Materials

$Zn(NO_3)_2.6H_2O$, $Al(NO_3)_3.9H_2O$ and ethanolamine were purchased from Himedia. Organic chemicals were purchased from Sigma Aldrich. All the chemicals were of high purity and used without further purification.

Synthesis of $ZnAl_2O_4$ nanoparticles

In a typical synthesis, the aqueous solutions of Zinc nitrate (1 M) and Aluminium nitrate (2 M) were mixed under vigorous stirring. The above homogeneous solution was stirred for 2 h followed by the addition of aqueous solution of ethanolamine (ethanolamine to water volume ratio of 6: 4) drop wise until the white precipitation stopped. The white precipitate was collected by filtration, washed with double distilled water, followed by acetone and it was then dried in oven at 80 °C overnight. The dried precursor was calcined at 300 °C, 500 °C and 700 °C with intermittent grinding.

Synthesis of copper supported on $ZnAl_2O_4$ nanoparticles

The above synthesized nano $ZnAl_2O_4$ was dispersed in known amount of copper nitrate solution under vigorous stirring. The stirring was continued for 6 h followed by filtration. The precipitate was washed with water to remove excess of copper nitrate, and was dried with acetone. The above precipitate was dispersed in water using ultrasonication and the dispersion was heated at 60 °C - 70 °C on hot plate under nitrogen atmosphere. To this dispersion, 2 ml of hydrazine hydrate was added drop wise under vigorous stirring under nitrogen atmosphere. Stirring was continued for 2 h. The obtained precipitate was collected by filtration followed by vacuum drying.

General synthetic procedure for $ZnAl_2O_4$ nanoparticles catalyzed propargylamines

Aldehyde (3 mmol), piperidine (3.3 mmol) and phenyl acetylene (3.6 mmol) were placed in round bottom flask along with nano $ZnAl_2O_4$ and stirred at 80 °C without solvent. The reaction was monitored by TLC. After completion, the reaction mixture was cooled and extracted with DCM solvent.

General synthetic procedure for Cu/ nano $ZnAl_2O_4$ catalyzed imidazo[1,2-a]pyridines

Aldehyde (3 mmol), 2-aminopyridine (3 mmol) and phenyl acetylene (3 mmol) were placed in round bottom flask along with Cu/nano $ZnAl_2O_4$. Nitrogen atmosphere was created in round bottom flask and the mixture was stirredat 80 °C without solvent under. The reaction was monitored by TLC. The reaction mixture was cooled and extracted with DCM solvent.

Characterization

Phase purity of the synthesized catalysts was determined by powder X-ray diffraction (XRD) patterns on Bruker X-ray diffractometer (D8 Advanced) with Cu Kα radiation (λ = 1.5406 Å) in the angle range of 2θ = 10 °-70 ° at room temperature. Specific surface area of the catalysts were measured from Nitrogen adsorption desorption isotherms on Micromeritics ASAP 2020 V3.00 H by Brunauer-Emmett-Teller (BET) method. Scanning Electron Microscopic (SEM) images and Energy Dispersive X-ray Analysis (EDX) data were obtained on JEOL JSM 7001F with BRUKER- QUNTAX Version 1.8.2. Morphology and crystallite size of the catalysts were determined by Transmission Electron microscopic (TEM) on JEOL 3010 instrument with UHR pole piece. Surface acidity of the synthesized nano $ZnAl_2O_4$ was analyzed by NH_3 temperature-programmed desorption (TPD) technique on Autochem 2910, Micromeritics instrument. 1.0 g of nano $ZnAl_2O_4$ was preheated in 30 mL high pure Helium flow at 120 ºC for 30 min at the heating rate of 10 ºC/min. Adsorption of NH_3 was done by passing 10% NH_3 in Helium gas at 30 mL/min flow through the sample for 30 min followed by purging pure Helium at 30 mL/min. NH_3 desorption was studied from 100 ºC to 650 ºC at 10 ºC/min utilizing thermal conductivity detector. CO_2 temperature-programmed desorption, TPD technique on the same instrument was used for analyzing surface basicity of nano $ZnAl_2O_4$. In a typical procedure, dried nano $ZnAl_2O_4$ powder (1.0 g) was pretreated in 50 mL high pure Helium flow at 200 ºC for 30 min. After which, the sample was saturated by CO_2 by passing 10% CO_2 in Helium gas with a flow rate of 75 mL/min at 30 ºC. The physisorbed CO_2 was removed by flushing Helium at 105 ºC over the sample for 2 h. TPD analysis was carried out from 100 ºC to 750 ºC at the heating rate of 10 ºC/min. XPS analysis of Cu/ZAO5 was performed on XM1000 spectrometer at room temperature with Al K radiation (h = 1486.6 eV) as the excitation source. C 1s 284.6 eV signal was referenced for the binding energy values. Concentration of leached metal ions of the catalyst after every cycle of the reaction was tested by Atomic Absorption Spectroscopic technique using Varian AA240 instrument. Organic compounds were confirmed by GC-MS.

Conclusion

In summary, we developed a facile, simple and efficient method for the synthesis of porous nano $ZnAl_2O_4$ with large surface area. The exploration of nano $ZnAl_2O_4$ and Cu/ nano $ZnAl_2O_4$ was found to be efficient catalysts for the synthesis of propargylamines and imidazo[1,2-a]pyridines respectively. The current protocols were simple, solvent- free, and they did not require any additive. Being cheap and reusable, nano $ZnAl_2O_4$ was found to be superior to the existing homogeneous and expensive noble metal catalysts.

Acknowledgement

Triveni Rajashekhar Mandlimath thanks CSIR for providing Senior Research Fellowship. She also thanks B. Uma Mahesh and M. Sathish Kumar for their valuable suggestions. The DST-FIST NMR facility at VIT University is greatly acknowledged (GC-MS). Authors thank Dr.R.Srinivasan, SSL, VIT for language editing.

Notes and references

*Chemistry Division – School of Advanced Sciences
VIT University, Vellore – 632014, Tamil Nadu, India
Fax: +914162243092; Tel: +914162244520; E-mail:sathiya_kuna@hotmail.com

S: Supporting Information

1 (a) E. Vedejs, J. W. Grissom, J. K. Preston, *J. Org. Chem.,* 1987, **52**, 3488-3489. (b) N. Gommermann, P. Knochel, *Chem. Commun.,* 2004, **20**, 2324-2325. (c) Q. Xu, E. Rozners, *Org. Lett.,* 2005, **7**, 2821-2824.

2 (a) F. Xiao, Y. Chen, Y. Liu, J. Wang, *Tetrahedron,* 2008, **64**, 2755-2761. (b) B. Yan, Y. Liu, *Org. Lett.,* 2007, **9**, 4321-4326. (c) E. S. Lee, H. S. Yeom, J. H. Hwang, S. Shin, *Eur. J. Org. Chem.,* 2007, **2007**, 3503-3507. (d) Y. Yamamoto, H. Hayashi, T. Saigoku, H. Nishiyama, *J. Am. Chem. Soc.,* 2005, **127**, 10804-10805. (e) D. F. Harvey, D. M. Sigano, *J. Org. Chem.,* 1996, **61**, 2268-2272.

3 (a). A. Jenmalm, W. Berts, Y. L. Li, K. Luthman, I. C. Bregh, U. Hacksell, *J. Org. Chem.,* 1994, **59**, 1139-1148. (b) Y. Imada, M. Yuasa, I. Nakamura, S. I. Murahashi, *J. Org. Chem.,* 1994, **59**, 2282-2284. (c) M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem.,* 1995, **60**, 4999-5004. (d) Trybulski, J. Eugene, Brabander, J. Herbert, 1994, *US5346910*.

4 (a) C. Binda, F. Hubalek, M. Li, Y. Herzig, J. Sterling, D. E. Edmondson, A. Mattevi, *J. Med. Chem.,* 2004, **47**, 1767-1774. (b) C. W. Olanow, *Neurology,* 2006, **66**, S69-S79. (c) M. Y. Falach, T. Amit, O. B. Am, M. B. H. Youdim, *FASEB J.,* 2003, 17, 2325- 2342.

5 V. Oldfield, G. M. Keating, C. M. Perry, *Drugs,* 2007, **67**, 1725-1747.

6 (a) M. Lhassani, O. Chavignon, J. M. Chezal, J. C. Teulade, J. P. Chapat, R. Snoeck, G. Andrei, J. Balzarini, E. D. Clercq, A. Gueiffier, *Eur. J. Med. Chem.,* 1999, **34**, 271-274. (b) K. C. Rupert, J. R. Henry, J. H. Dodd, S. A. Wadsworth, D. E. Cavender, G. C. Olini, B. Fahmy, J. J. Siekierka, *Bioorg. Med. Chem. Lett.,* 2003, **13**, 347-350. (c) L. Almirante, L. Polo, A. Mugnaini, E. Provinciali, P. Rugarli, A. Biancotti, A. Gamba, W. Murmann, *J. Med. Chem.,* 1965, **8**, 305-312. (d) Y. Kastura, S. Nishino, Y. Inoue, M. Tomoi, H. Takasugi, *Chem. Pharm. Bull.,* 1992, **40**, 371-380. (e) Y. Rival, G. Grassy, G. Michel, *Chem. Pharm. Bull.,* 1992, **40**, 1170 - 1176.

7 (a) A. N. Jain, *J. Med. Chem.,* 2004, **47**, 947-961. (b) N. Hsu, S. K. Jha, T. Coleman, M. G. Frank, *Behav. Brain Res.,* 2009, **201**, 233-236. (c) G. Trapani, M. Franco, L. Ricciardi, A. Latrofa, G. Genchi, E. Sanna, F. Tuveri, E. Cagetti, G. Biggio, G. Liso, *J. Med. Chem.,* 1997, **40**, 3109-3118. (d) S. M. Hanson, E. V. Morlock, K. A. Satyshur, C. Czajkowski, *J. Med. Chem.,* 2008, **51**, 7243-7252.

8 S. Takizawa, J. I. Nishida, T. Tsuzuki, S. Tokito, Y. Yamashita, *Chem. Lett.,* 2005, **34**, 1222-1223; b) S. Takizawa, J. I. Nishida, Y. Yamashita, T. Tsuzuki, S. Tokito, *Mol. Cryst. Liq. Cryst.,* 2006, **455**, 381-385; c) S. Takizawa, J. I. Nishida, T. Tsuzuki, S. Tokito, Y. Yamashita, *Inorg. Chem.,* 2007, **46**, 4308- 4319.

9 (a) M. E. Jung, A. Huang, *Org. Lett.,* 2000, **2**, 2659-2661, (b) S. S. Patil, S. V. Patil, V. D. Bobade, *Syn. Lett.,* 2011, **8**, 1157-1159. (c) W. Ryan, C. Ainsworth, *J. Org. Chem.,* 1961, **26**, 1547-1550. (d) T. Takahashi, F. Bao, G. Gao, M. Ogasawara, *Org. Lett.,* 2003, **5**, 3479-3481. (e) T. Harada, T. Fujiwara, K. Iwazaki, A. Oku, *Org.*

Lett., 2000, **2**, 1855-1857, (f) A. Tuulmets, V. Pallin, J. T. Taul, P. Burk, K. Raie, *J. Phys. Org. Chem.,* 2002, **15**, 701-705.

10 (a) E. Ramu, R. Varala, N. Sreelatha, S. R. Adapa, Tetrahedron Lett., 2007, 48, 7184-7190. (b) C. Wei, Z. Li, C. J. Li, *Org. Lett.,* 2003, **5**, 4473-4475. (c) C. Wei, C. J. Li, *J. Am. Chem. Soc.,* 2003, **125**, 9584-9585. (d) W. W. Chen, R. V. Nguyen, C. J. Li, *Tetrahedron Lett.,* 2009, **50**, 2895-2898, (e) D. S. Raghuvanshi, K. N. Singh, *Syn. Lett.,* 2011, **3**, 373-377. (f) Y. Zhang, P. Li, M. Wang, L. Wang, *J. Org. Chem.,* 2009, **74**, 4364-4367. (g) J. S. Yadav, B. V. S. Reddy, A. V. H. Gopal, K. S. Patil, *Tetrahedron Lett.,* 2009, **50**, 3493-3496. (h) Q. Zhang, J. X. Chen, W. X. Gao, J. C. Ding, H. Y. Wu, *Appl. Organometal. Chem.,* 2010, **24**, 809-812. (i) S. Samai, G. C. Nandi, M. S. Singh, *Tetrahedron Lett.,* 2010, **51**, 5555-5558. (j) Li, P. Hua, Wang, Lei, *Chin. J. Chem.,* 2005, **23**, 1076-1080.

11 (a) K. K. Y. Kung, V. K. Y. Lo, H. M. Ko, G. L. Li, P. Y. Chan, K. C. Leung, Z. Zhou, M. Z. Wang, C. M. Che, M. K. Wonga, *Adv. Synth. Catal.,*2013, **355**, 2055-2070. (b) V. K. Y. Lo, K. K. Y. Kung, M. K. Wong, C. M. Che, *J. Organometal. Chem.,* 2009, **694**, 583-591. (c) V. K. Y. Lo, Y. Liu, M. K. Wong, C. M. Che, *Org. Lett.,* 2006, **8**, 1529-1532. (d) G. Villaverde, A. Corma, M. Iglesias, F. Sánchez, *ACS Catal.,* 2012, **2**, 399-406.

12 Y. Zhang, A. M. Santos, E. Herdtweck, J. Minkbc, F. E. Kuhn, *New J. Chem.,* 2005, **29**, 366-370.

13 (a) M. Kidwai, V. Bansal, A. Kumar, S. Mozumdar, *Green Chem.,* 2007, **9**, 742-745. (b) W. Yan, R. Wang, Z. Xu, J. Xu, L. Lin, Z. Shen, Y. Zhoua, *J. Molecul. Catal. A: Chem.,* 2006, **255**, 81-85.

14 X. Zhang, A. Corma, *Angew. Chem. Int. Ed.,* 2008, **47**, 4358-4361.

15 B. J. Borah, S. J. Borah, K. Saikia, D. K. Dutta, *Catal. Sci. Technol.,* 2014, **4**, 4001-4009.

16 R. Mallampati, S. Valiyaveettil, *ACS Sustain. Chem. Eng.,* 2014, **2**, 855-859.

17 F. Movahedi, H. Masrouri, M. Z. Kassaee, *J. Molecul. Catal. A: Chem.,* 2014, **395**, 52-57.

18 K. Layek, R. Chakravarti, M. L. Kantam, H. Maheswarana, A. Vinu, *Green Chem.,* 2011, **13**, 2878-2887.

19 P. Li, L. Wang, Y. Zhang, M. Wang, *Tetrahedron Lett.,*2008, 49, 6650-6654.

20 L. Abahmane, J. M. Kçhler, G. A. Grob, *Chem. Eur. J.,* 2011, **17**, 3005-3010.

21 B. J. Borah, S. J. Borah, L. Saikia, D. K. Dutta, *Catal. Sci. Technol.,* 2014, **4**, 1047-1054.

22 J. S. Yadav, B. V. S. Reddy, C. S. Reddy, K. Rajasekhar, *J. Org. Chem.,* 2003, **68**, 2525-2527.

23 H. Guo, X. Liu, Q. Xie, L. Wang, D. L. Peng, P. S. Branco, M. B. Gawande, *RSC Adv.,* 2013, **3**, 19812-19815.

24 M. K. Patil, M. Keller, B. M. Reddy, P. Pale, J. Sommer, *Eur. J. Org. Chem.,* 2008, **2008**, 4440-4445.

25 C. Mukhopadhyay, S. Rana, *Catal. Comm.,* 2009, **11**, 285-289.

26 K. D. Bhatte, D. N. Sawant, K. M. Deshmukh, B. M. Bhanage, *Catal. Comm.,* 2011, 16, 114-119.

27 J. Dulle, K. Thirunavukkarasu, M. C. M. Hazeleger, D. V. Andreeva, N. R. Shiju, G. Rothenberg, *Green Chem.,* 2013, **15**, 1238-1243.

28 I. Luz, F. X. L. Xamena, A. Corma, *J. Catal.,* 2012, 285, 285-291.

29 N. Chernyak, V. Gevorgyan, *Angew. Chem. Int. Ed.,* 2010, **49**, 2743-2746.

30 B.V. S. Reddy, P. S. Reddy, Y. J. Reddy, J. S. Yadav, *Tetrahedron Lett.,*2011, **52**, 5789–5793.

31 S. K. Guchhait, A. L. Chandgude, G. Priyadarshani, *J. Org. Chem.,* 2012, **77**, 4438-4444.

32 I. R. Siddiqui, P. Rai, Rahila, A. Srivastava, S. Shamim, *Tetrahedron Lett.,* 2014, **55**, 1159-1163.

33 S. Mishra, R. Ghosh, *Synthesis,* 2011, **21**, 3463-3470.

34 P. Liu, L. Fang, X. Lei, G. Lin, *Tetrahedron Lett.,* 2010, **51**, 4605-4608.

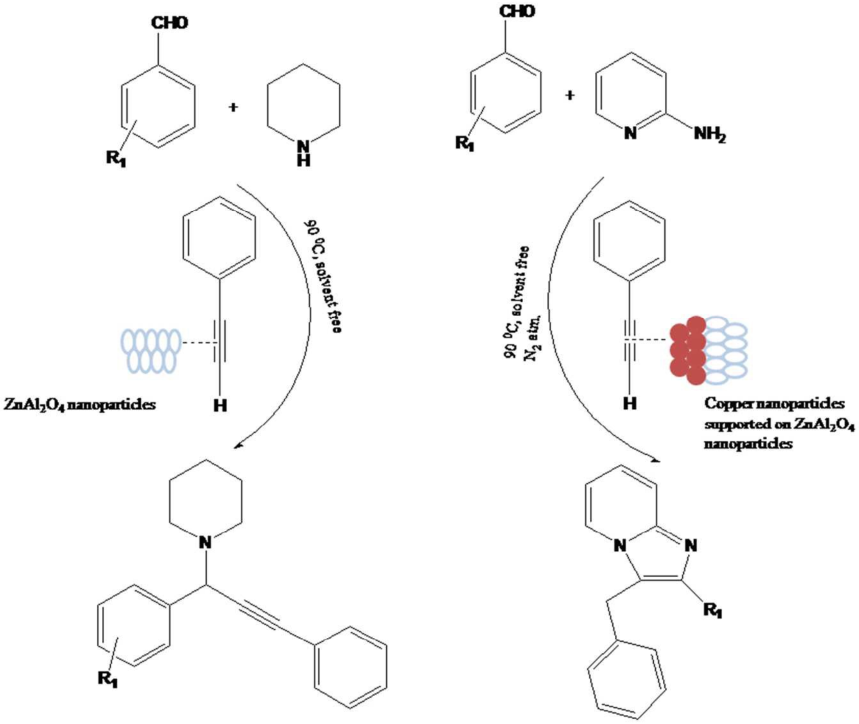
35 P. Liu, C. L. Deng, X. Lei, G. Lin, *Eur. J. Org. Chem.,* 2011, 7308-7316.

36 T. R. Mandlimath, B. Umamahesh, K. I. Sathiyanarayanan, *J. Mol. Catal. A: Chem.,* 2014, **391**, 198-207.

37 B. Umamahesh, T. R. Mandlimath, K. I. Sathiyanarayanan, *RSC Adv.,* 2014, **5**, 6578-6587.

38 Q. Liu, L. Wang, C. Wang, W. Qu, Z. Tian, H. Ma, D. Wang, B. Wang, Z. Xu, *Appl. Catal., B,* 2013, **136-137**, 210-217.

39 S. Velu, K. Suzuki, Chinnakonda, S. Gopinath, H. Yoshida, T. Hatoor, *Phys. Chem. Chem. Phys.*, 2002, **4**, 1990-1999.



254x190mm (96 x 96 DPI)