ACS Sustainable Chemistry & Engineering

Research Article

pubs.acs.org/journal/ascecg

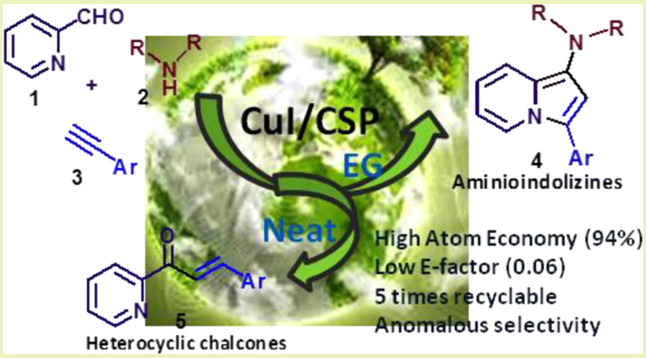
One-Pot Synthesis of Aminoindolizines and Chalcones Using CuI/CSP Nanocomposites with Anomalous Selectivity under Green Conditions

U. Chinna Rajesh, Gunjan Purohit, and Diwan S. Rawat*

Department of Chemistry, University of Delhi, Delhi 110007, India

Supporting Information

ABSTRACT: CuI/CSP nanocomposites were found to be efficient and recyclable nanocatalysts for one-pot synthesis of aminoindolizines via A3 coupling reaction in the presence of ethylene glycol (EG) as a recyclable solvent. In contrast, chalcones were isolated when the reaction was performed in the presence of secondary amines such as piperidine, 3-methylpiperidine, pyrrolidine, and piperazine under solvent free conditions. The CuI/CSP was recycled for five times without significant loss in its catalytic activity. The anomalous selectivity in the formation of aminoindolizines and chalcones was dependent on solvents and secondary amines used for the reaction. The present methodology is facile and follows green principles with higher atom economy (94%) and smaller *E*-factor (0.06).



KEYWORDS: *Aminoindolizines, A3 Coupling reaction, Chalcones, Green chemistry, E-Factor and atom economy*

■ INTRODUCTION

Carbon spheres (CSP) have been considered as sustainable catalyst supports for various metal NPs with specific catalytic properties and greatly widen their utility in the fields of nanocatalysis.[1] The CSP could be prepared by various methods,[2,3] and the hydrothermal carbonization from glucose as a carbon source without using any template is the simple and green method.[4,5] During the hydrothermal carbonization process, glucose was first polymerized as a polysaccharide in water, and then formed small spheres with inner cores of a completely carbonized hydrophobic carbon layer and the outer surface with an incompletely carbonized hydrophilic polysaccharide layer.[6] Amphiphilic carbon spheres (CSP) are readily dispersible in various solvents of different polarities without any prior surface modifications.[7] The outer polysaccharide surface of CSP has many functional groups such as hydroxyl, carboxylic, and aldehyde groups, which are suitable for the stabilization of various metal NPs.[8−11] Recently, Pd/CSP composites were found to be efficient amphiphilic catalysts for Heck, Ullmann, Suzuki−Miyaura, and selective partial hydrogenation reactions in aqueous medium.[12−14] To date, copper/CSP composites have been reported for very limited applications such as surface-enhanced Raman scattering substrate,[15] efficient anodes for lithium-ion batteries,[16] or CSP as a template for synthesis of porous CuO hollow spheres.[17,18] However, although CuI alone[19] or Cu NPs stabilized on various supported materials[20] has been found potential applications in the field of nanocatalysis, CuI/CSP composites have not been investigated as catalysts for the multicomponent organic synthesis.

Multicomponent reactions (MCR) promoted by recyclable nanocatalysts under green reaction conditions provide an efficient tool for the sustainable synthesis of heterocycles.[21] Indolizines are unique N-fused heterocycles and have been found in pharmacological relevance molecules with a wide range of biological activities (Figure 1).[22]

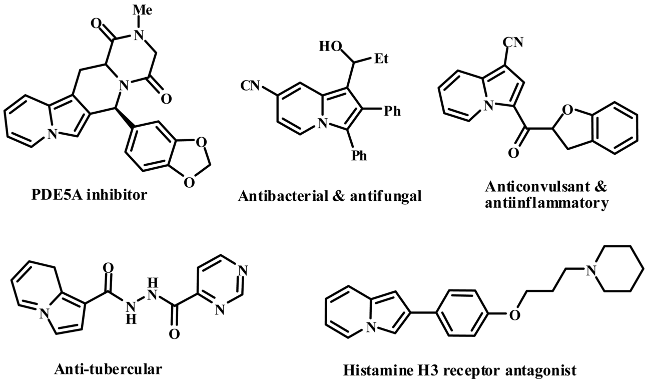


Figure 1. Biologically active indolizine scaffolds.

Received: April 20, 2015
Revised: August 8, 2015
Published: September 4, 2015

DOI: 10.1021/acssuschemeng.5b00701
ACS Sustainable Chem. Eng. 2015, 3, 2397−2404

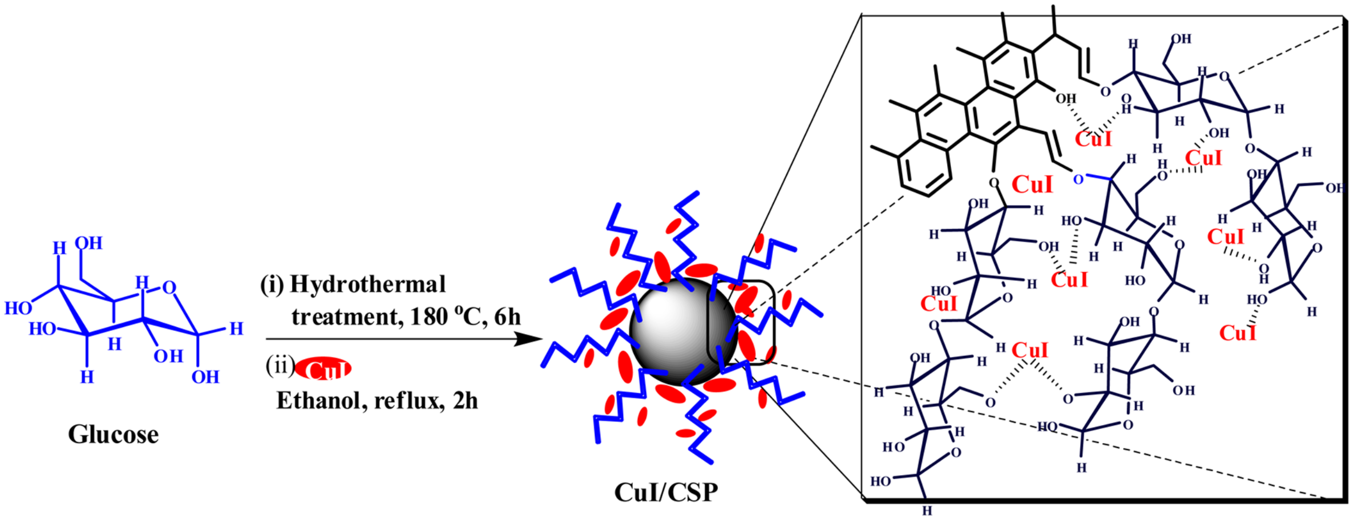


Figure 2. Schematic representation for the preparation of CuI/CSP nanocomposites.

Among the various known methodologies for the synthesis of indolizines,[23−27] one-pot three component reaction between pyridine-2-carboxaldehyes, secondary amines, and phenylacetylenes via A3 coupling followed by cycloisomerization is one of the efficient approaches. To date, very limited catalytic systems have been developed for the synthesis of aminoindolizines via A3 coupling strategy.[28−34] Alonso et al. reported the use of CuO/Cu_2O/activated charcoal (Cu NPs/C) as a heterogeneous catalyst for solvent-dependent synthesis of indolizines and chalcones.[28] However, this method has advantages over the reported homogeneous catalysis such as usage of low catalyst loading, simple work up procedure etc. But it has a drawback of catalyst recyclability due to the leaching of Cu NPs from its carbon support and usage of toxic organic solvents. Still, there is a need for developing truly recyclable heterogeneous catalysts under green reaction conditions. With this background, and as a part of our ongoing research toward green chemistry and nanocatalysis,[36−44] we herein report the facile one-pot synthesis of aminoindolizines using CuI/CSP nanocomposites with anomalous selectivity under green conditions.

■ RESULTS AND DISCUSSION

CuI/CSP nanocomposites were synthesized by refluxing the mixture of CuI and carbon spheres (CSP) in ethanol as shown in Figure 2. The CSP were prepared by hydrothermal carbonization of glucose at 180 °C by following the literature procedure.[1] Next, the CuI was stabilized on polysaccharide surface of CSP by mixing of CuI and CSP in equal ratios in ethanol at conventional reflux conditions (Figure 2).

The CuI/CSP nanocomposites were characterized by using various techniques such as powder X-ray diffraction (PXRD), Fourier transform infrared spectroscopy (FT-IR), scanning electronic microscopy (SEM), transmission electronic microscopy (TEM), thermal gravimetric analysis (TGA), X-ray photoelectron spectra (XPS), inductively coupled plasma atomic emission spectroscopy (ICP-AES), etc. The powder XRD of CuI/CSP composites revealed the existence of crystalline CuI with phases (111), (200), (220), (311), (222), (400), (331), and (420) of corresponding diffraction peaks at 2θ are 25.36, 29.36, 42.16, 49.89, 52.29, 61.08, 67.48, and 69.48, respectively (JCPDS, 06-0246), as shown in Figure 3. The average crystalline size of CuI NPs was calculated by using Scherrer equation and found to be 13 nm.

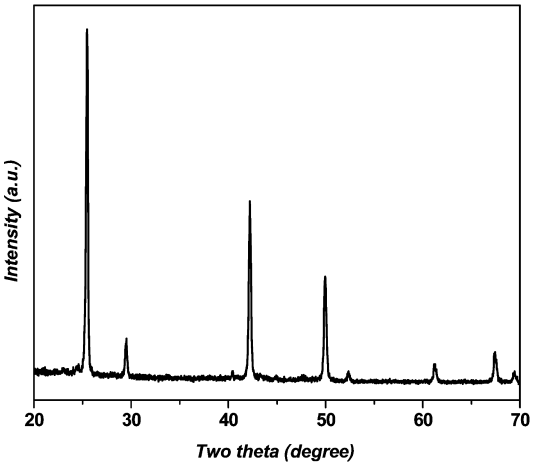


Figure 3. PXRD of CuI/CSP composites.

The functional groups of CSP and CuI/CSP composites were characterized by using FT-IR spectra as shown in Figure 4.[6] The broad band at 3405 cm^{-1} corresponds to the hydroxyl functionalities on the surface of CSP. The presence of carbonyl (C=O) and unsaturated (C=C) groups were conformed from the bands at 1701 and 1614 cm^{-1} respectively, and these groups support the concept of aromatization of glucose during hydrothermal treatment. Moreover, the presence of −C—OH (1190 cm^{-1}), and glycosidic −C—O—C− linkages (1099 cm^{-1}) were also conformed from FT-IR technique as shown in Figure 4. The existences of these functional groups on carbon framework of CSP improve the stability of CuI NPs on its surface.

The surface and internal morphologies of CuI/CSP nanocomposites were characterized from SEM and TEM, respectively (Figure 5). Figure 5a shows the surface morphology of CSP as spheres with various sizes, and the SEM image of CuI/CSP show the existence of spheres, distorted spheres, and cubes of various size ranges from 2 to 8 μm (Figure 5b). It is also showing the existence of CuI NPs on the surface and in between the various carbon spheres. The

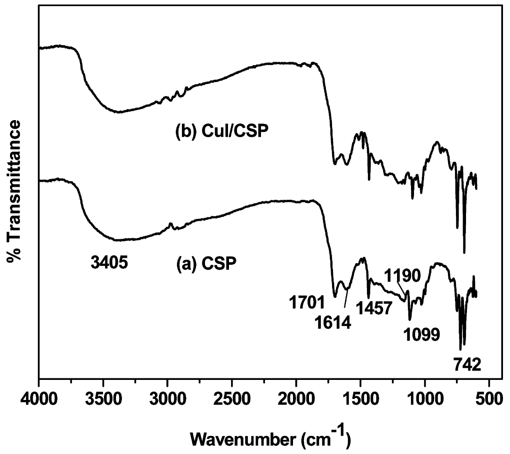


Figure 4. FT-IR of (a) CSP and (b) CuI/CSP nanocomposites.

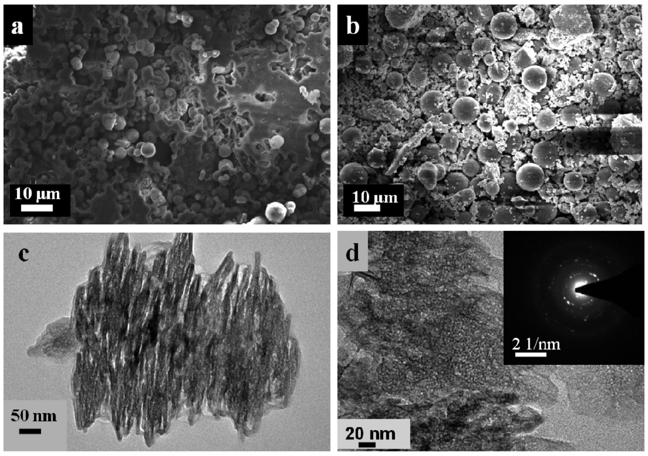


Figure 5. SEM images of (a) CSP and (b) CuI/CSP; and TEM images (c, d) of CuI/CSP (inset of d is SAED of CuI).

internal morphology of CuI/CSP reveals that the assembling of porous rods in the spherical shape and the length of these rods varies from 100 to 320 nm (Figure 5c). The porous and crystalline nature of carbon and CuI NPs (inset of Figure 5d) were conformed from TEM and SAED, respectively (Figure 5d).

The oxidation state of copper in CuI/CSP composites was determined from X-ray photoelectron spectra (XPS) as shown in Figure 6. The presence of Cu(+1) was conformed from the binding energies at 932 and 620 eV corresponds to $Cu(+1)_{2p}$ and $I(-1)_{3d}$, respectively.[45] The binding energy peak at 284 eV corresponds to carbon content (C_{1S}) of CSP and (see the Supporting Information).[46]

The thermal decomposition of CuI/CSP composites was studied by TGA and DTG analysis in the temperature range from 100 to 800 °C at the rate of 10 °C per minute under nitrogen atmosphere as shown in Figure 7. The weight loss at the temperature range 200−270 °C is about 13.59% due to the loss of surface hydroxyls and water molecules in the CSP of composite nanoparticles. In the second step, the maximum weight loss is about 30.7% at the temperature range 350−360 °C, which due to the combustion of amorphous carbon. The final weight loss of 48.4% at the temperature range from 390 to 560 °C is may be a response to decomposition of CuI and some residual carbon (Figure 7).

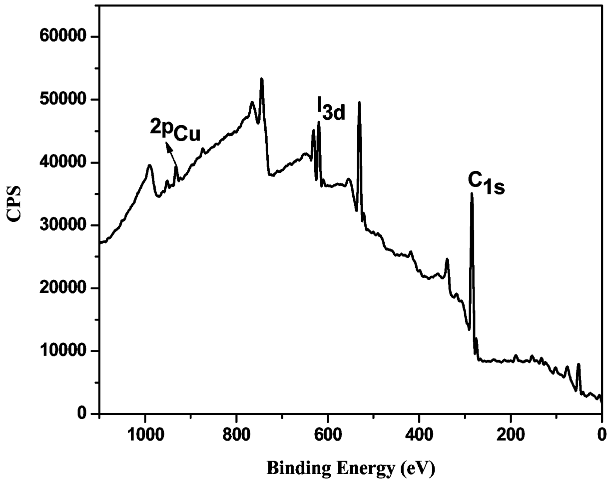


Figure 6. X-ray photoelectron spectrum (XPS) of CuI/CSP nanocomposites.

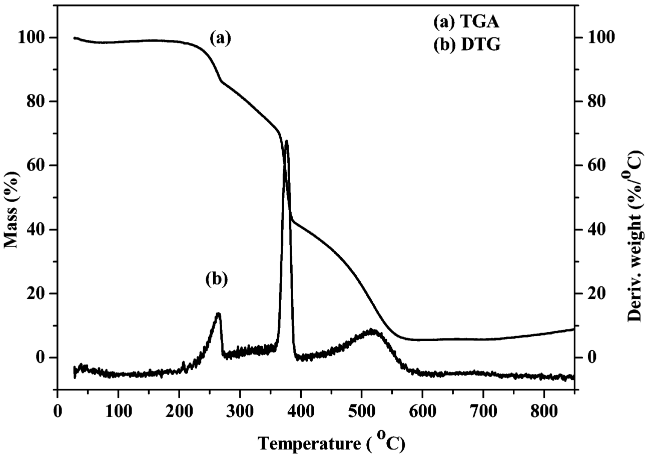


Figure 7. TGA and DTG analysis of CuI/CSP composites.

The EDAX elemental analysis of CuI/CSP composites reveals the presence of Cu in 14.4 at. % and iodide was found to be 11.7 at. % as shown in Figure 8. The sum of copper (Cu^{1+}) and iodide (I^{-}) was calculated as 26.1 at. % and the remaining approximately 74.0 at. % mainly belongs to carbon and polysaccharide functional groups (carbon 68.16 at. % and oxygen 5.74 at. %). The average weight percentage of copper in CuI/CSP was found to be 19.10 wt %. The weight percentage of copper in CuI/CSP composites was calculated from ICP-AES analysis and found to be 19.70 wt %, which is almost inconsistent with EDAX analysis.

CuI/CSP Composites as Nanocatalysts for Synthesis of Aminoindolizine. Initially, the model reaction was performed among pyridine-2-carboxaldehyde (**1a**), morpholine (**2a**), and phenylacetylene (**3a**) using 5 mg of CuI/CSP catalyst in the presence various solvents at different temperatures as shown in Table 1.

To our delight, the desired aminoindolizine (**4aa**) was obtained selectively in excellent yield in the presence of either all solvents such as toluene, DMSO, DMF, water, glycerin, EG or neat conditions at temperatures from 60 to 100 °C (Table 1, entries 1−9). However, the reactions were sluggish at room temperature in the presence of either EG or neat conditions (entry 10). The model reaction was performed either in the presence of bulk CuI alone or physical mixture of bulk CuI and

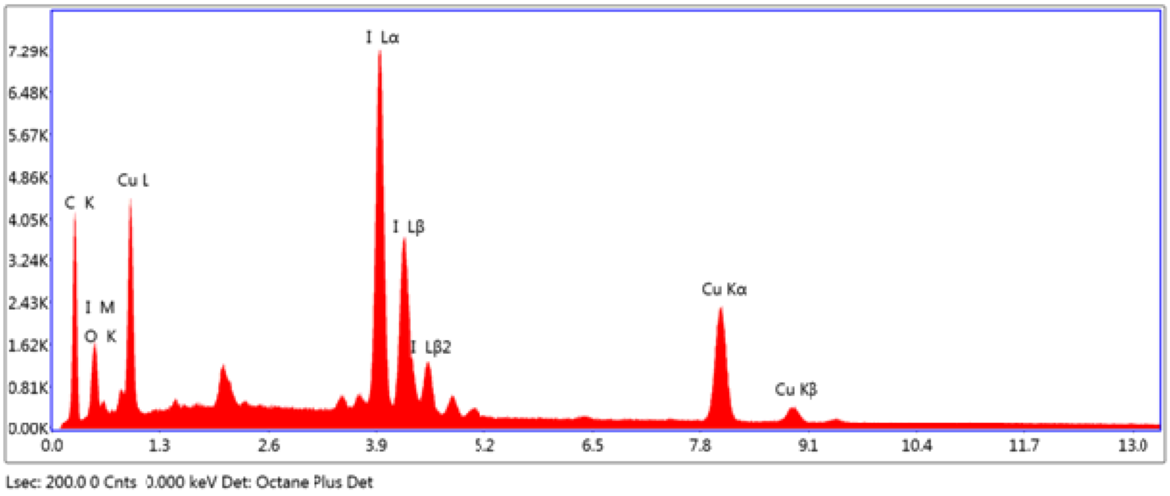
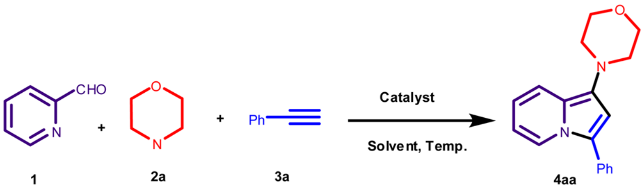


Figure 8. EDAX elemental analysis of CuI/CSP composites.

Table 1. Optimization Study for CuI/CSP Catalyzed Synthesis of Aminoindolizine (4aa)[a]



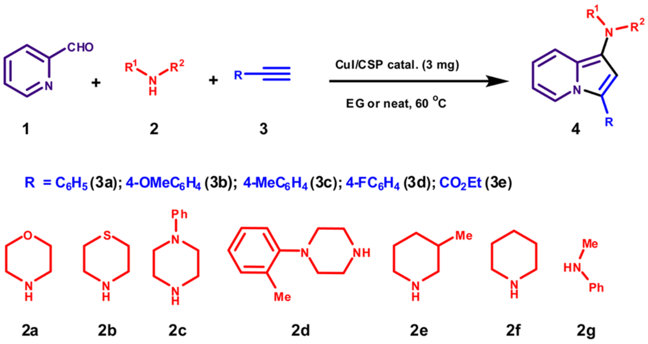
entry	catalyst	solvent	temp. (°C)	time (h)	yield of **4aa** (%)
1	CuI/CSP	toluene	100	3	83
2	CuI/CSP	DMSO	100	3	86
3	CuI/CSP	DMF	100	3	82
4	CuI/CSP	water	100	3	90
5	CuI/CSP	glycerin	100	2	88
6	CuI/CSP	EG	100	0.5	94
7	CuI/CSP	EG	80	0.5	94
8	CuI/CSP	EG	60	0.5	94
9	CuI/CSP	neat	60	1	90
10	CuI/CSP	EG/neat	rt	10	trace
11	CuI (bulk)	EG	60	10	60
12	CuI (bulk) + CSP	EG	60	6	75
13	CSP	EG	60	24	no product
14	no catalyst	EG	60	24	no product

[a] Reaction conditions: pyridine-2-carboxaldehye **1** (1 mmol), morpholine **2a** (1 mmol), phenylacetylene **3** (1 mmol), and CuI/CSP catalyst (5 mg), solvent (3 mL) were stirred at appropriate temperature.

CSP to afford the product in moderate to good yields in longer reaction times of 6−10 h (entries 11 and 12). But when the reaction was performed using either CSP alone as a catalyst or without any catalyst, the product formation was not observed even after 24 h (entries 13 and 14). The results reveal that EG and neat conditions at 60 °C were the best to afford the product (**4aa**) in excellent yield in short reaction time (Table 1, entries 6−9).

The generality of the present method was studied with the wide range of substrates including pyridine-2-carboxaldehye, various alkynes including phenylacetylenes (**3a**−**3d**) and ethyl propiolate (**3e**), and secondary amines such as morpholine, thiomorpholine, phenylpiperazine, 1-(o-tolyl)piperazine, 3-metylpiperidine, piperidine, and *N*-methylaniline as shown in Scheme 1.

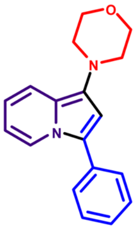
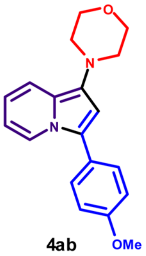
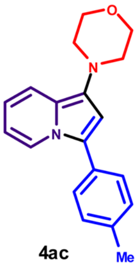
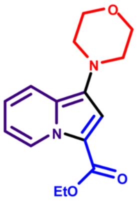
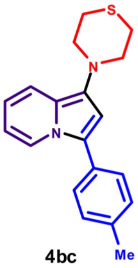
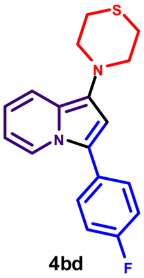
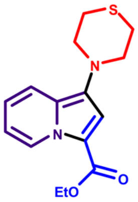
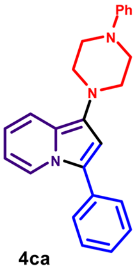
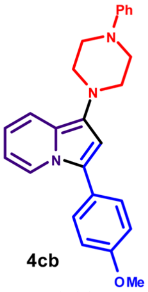
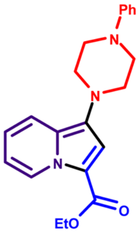
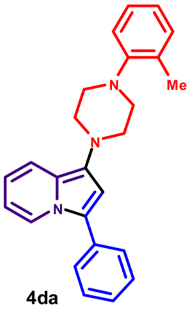
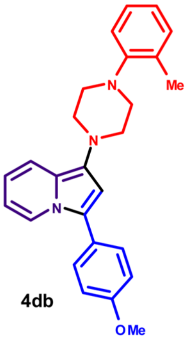
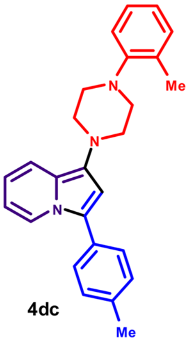
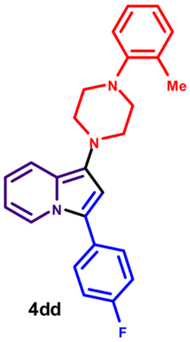
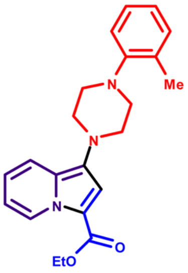
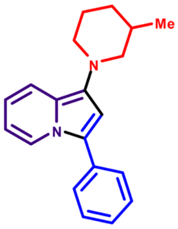
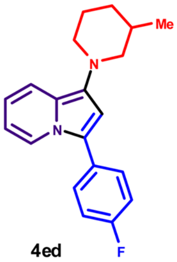
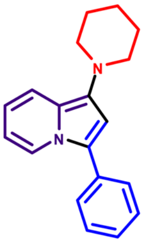
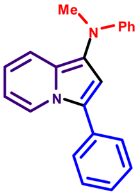
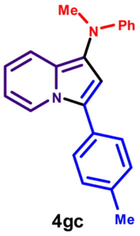
Scheme 1. CuI/CSP Catalyzed One-Pot Synthesis of Aminoindolizine Derivatives



To our delight, almost all screened substrates underwent smooth cycloisomerization to afford the aminoindolizines exclusively in 75% to 95% yields in EG solvent as shown in Table 2. However, it is interesting to see that the product formation was dependent on secondary amines under solvent free conditions. Aminoindolizines were obtained as major products in the presence of secondary amines such as morpholine (**2a**), thiomorpholine (**2b**), phenylpiperazine (**2c**), 1-(o-tolyl)piperazine (**2d**), and *N*-methylaniline (**2g**) (Table 2). Heterocyclic chalcones (**5a**−**5c**) were obtained as major products in the presence of 3-metylpiperidine (**2e**), piperidine (**2f**), pyrrolidine (**2h**), and piperazine (**2i**) as shown in Table 4.

With these interesting results in our hand, we further investigated the effect of solvents on the selectivity of chalcone and aminoindolizine formation in the presence of piperidine as shown in Table 3. Heterocyclic chalcone **5a** was obtained in 75% and 90% conversions with exclusive *E*-stereochemistry in the presence of water and neat conditions, respectively (Table 3, entries 1 and 5). Aminoindolizine (**4fa**) was observed in 90% and 85% conversions in the presence of EG and PEG respectively (entries 2 and 3). However, the conversions of chalcone (**5a**) and aminoindolizine (**4fa**) were observed in the equal ratio (50:50%) in the presence of glycerin (entry 4).

Table 2. CuI/CSP Catalyzed Synthesis of Aminoindolizine Derivatives in EG and Solvent Free Conditions

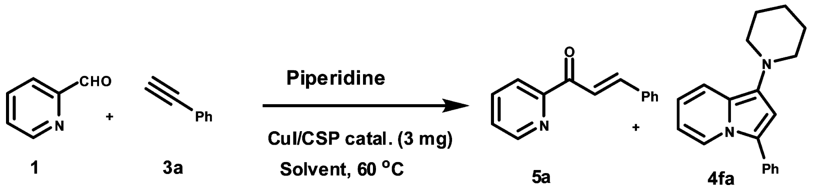
 **4aa** EG; Yield, 92% Neat; Yield, 90%	 **4ab** EG; Yield, 92% Neat; Yield, 89%	 **4ac** EG; Yield, 91% Neat; Yield, 95%	 **4ae** EG; Yield, 90% Neat; Yield, 85%	 **4bc** EG; Yield, 89% Neat; Yield, 83%
 **4bd** EG; Yield, 90% Neat; Yield, 75%	 **4be** EG; Yield, 95% Neat; Yield, 82%	 **4ca** EG; Yield, 85% Neat; Yield, 88%	 **4cb** EG; Yield, 89% Neat; Yield, 86%	 **4ce** EG; Yield, 92% Neat; Yield, 84%
 **4da** EG; Yield, 91% Neat; Yield, 76%	 **4db** EG; Yield, 93% Neat; Yield, 80%	 **4dc** EG; Yield, 88% Neat; Yield, 81%	 **4dd** EG; Yield, 92% Neat; Yield, 86%	 **4de** EG; Yield, 95% Neat; Yield, 82%
 **4ea** EG; Yield, 85% Neat; Yield, 20%	 **4ed** EG; Yield, 87% Neat; Yield, 18%	 **4fa** EG; Yield, 75% Neat; Yield, 10%	 **4ga** EG; Yield, 92% Neat; Yield, 80%	 **4gc** EG; Yield, 90% Neat; Yield, 83%

When the reaction was performed in the absence of catalyst, the reaction was sluggish (Table 3, entry 6).

Furthermore, we studied the effect of remaining secondary amines such as 3-metylpiperidine (**2e**), pyrrolidine (**2h**), and piperazine (**2i**) on the selectivity of product formation under solvent free condition as shown in Scheme 2 and Table 4. To our delight, all these secondary amines (**2e**, **2f 2h**, **2i**) afforded chalcones **5a**, **5b**, and **5c** in good to excellent yields of 75−93% (Table 4).

Next, the green and sustainability factors such as atom economy and *E*-factor of present method were calculated for the model reaction between pyridine-2-carboxaldehyde (**1a**), morpholine (**2a**), and phenylacetylene (**3a**) to afford the aminoindolizine (**4aa**). The results indicate that the present method follows green chemistry principles with smaller *E*-factor as 0.06 and high atom economy (AE) as 94% (see the Supporting Information for calculations). Moreover, the comparative study of CuI/CSP catalyst with the reported methods clearly indicates the superiority of present method in

Table 3. Effect of Solvents on the Selectivity of Chalcone (5a) and Aminoindolizine (4fa)[a]



entry	solvent	time (min)	conversions (%)[b]	
			5a	4fa
1	water	180	75	15
2	EG	30	trace	90
3	PEG	60	trace	85
4	glycerin	120	50	50
5	neat	45	90	10
6	neat[c]	120		

[a] Reaction conditions: pyridine-2-carboxaldehye **1** (1 mmol), piperidine **2d** (1 mmol), phenylacetylene **3a** (1 mmol), and CuI/CSP catalyst (5 mg) were stirred under neat conditions at 60 °C. [b] Conversions are calculated from ^1H NMR of reaction mixtures. [c] Reaction was performed without catalyst.

Scheme 2. Synthesis of *E*-Selective Heterocyclic Chalcones

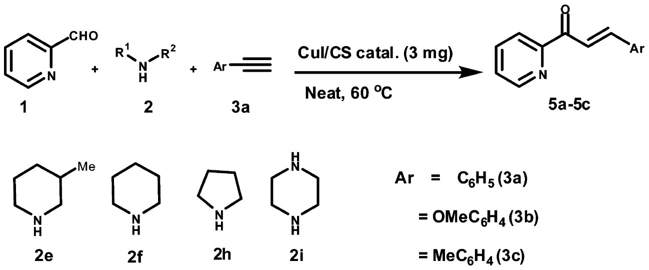


Table 4. CuI/CSP Catalyzed Synthesis of Chalcones under Solvent Free Conditions

entry	amines (2)	Ar (3)	chalcones (5)	yield of 5 (%)
1	**2e**	C_6H_5	**5a**	78
2	**2e**	$OMeC_6H_4$	**5b**	75
3	**2f**	C_6H_5	**5a**	90
4	**2f**	$OMeC_6H_4$	**5b**	85
7	**2f**	MeC_6H_4	**5c**	87
8	**2h**	C_6H_5	**5a**	97
9	**2i**	C_6H_5	**5a**	79
10	**2i**	$OMeC_6H_4$	**5b**	75

[a] Reaction conditions: pyridine-2-carboxaldehye **1** (1 mmol), amines **2d**/**2e**/**2f** (1 mmol), phenylacetylenes **3** (1 mmol), and CuI/CSP catalyst (5 mg) were stirred under neat conditions at 60 °C.

Table 5. Comparative Study of Various Catalysts for the Synthesis of Aminoindolizine (4aa)

S. No.	catalyst	solvent	yield of 4aa (%)	refs	recycle of catalyst
1	ZnI_2	toluene	90	29	no
2	Cu NPs/C	DCM	74	28, 30	no
3	CuCl	PEG	96	31	no
4	CuI[a]	toluene	96	32	no
5	$Fe(acac)_3$	TBAOH DMSO	83	33	no
6	$AgBF_4$	toluene	89	34	no
7	$NaAuCl_4{\cdot}2H_2O$	neat	95	35	no
8	CuI/CSP	EG	92	present study	yes

[a] CuI reported as homogeneous catalyst for coupling reaction among methyl *N*-allyl-1-formyl-9H-*β*-carboline-3-carboxylate, morpholine, and phenyl acetylene.

terms of selectivity, recyclability, and green and mild reaction conditions as shown in Table 5.

The plausible mechanism for the formation of aminoindolizine via A3 coupling followed by cycloisomerization is well-known in the literature.[28−34] Very recently, Alonso et al. reported synthetic and mechanistic studies on the solvent-dependent Cu NPs/C catalyzed formation of aminoindolizine and chalcones.[28] They have demonstrated the formation of propargyl amines (A3 product) as intermediate for aminoindolizine using GC−MS analysis. The X-ray structure of chalcone and reaction mechanism for the formation of chalcone was determined from isotopic-labeling experiments.[28] To understand the detailed mechanism, we would be pursuing the theoretical studies for CuI/CSP catalyzed formation of aminoindolizine and chalcones with dependence on secondary amines and solvents.

We performed recyclability experiments to study the advantage of the CuI/CSP nanocomposite catalyst over the physical mixture of CuI (bulk) and CSP. The recyclability of CuI/CSP catalyst was studied for a model reaction to afford aminoindolizine (**4aa**) in the presence of EG under optimized reaction condition as shown in Figure 9. After completion of reaction, water was added to the reaction mixture to recover EG from aqueous layer. Next, ethanol was added to the reaction mixture to separate the solid CuI/CSP NPs from organic layer by centrifuge. The catalyst was washed several times with ethanol and dried at 90 °C in oven for 10 h. The recovered CuI/CSP catalyst and EG solvent were reused in model reaction to afford the product in 90% yield, and the procedure was repeated for four more times and it was found that there was no significant loss in its catalytic activity (Figure 9). But the reutilization of physical mixture was inefficient due to leaching of CuI or catalyst poisoning.[28]

Furthermore, we studied the heterogeneity of model reaction for the synthesis of **4aa** in water as a solvent at 90 °C by hot filtration test experiment. The reaction was stopped at 50% conversion of starting materials that is in 30 min and filtered out the catalyst from reaction mixture. The filtrate was further

DOI: 10.1021/acssuschemeng.5b00701
ACS Sustainable Chem. Eng. 2015, 3, 2397−2404

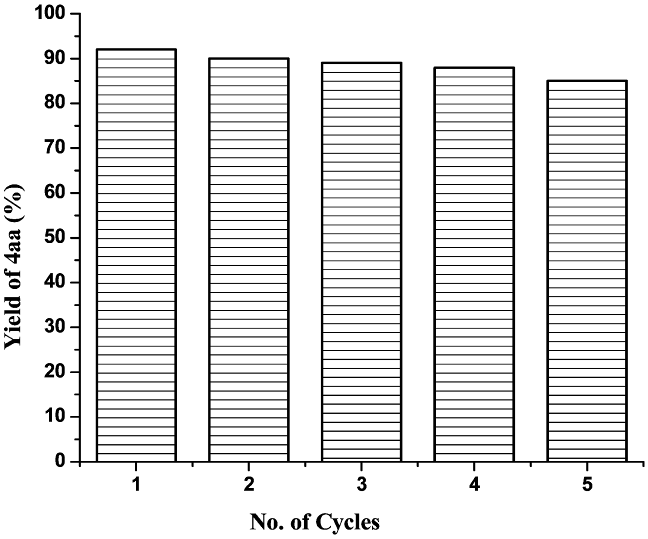


Figure 9. Recyclable study of CuI/CSP catalyst for synthesis of (**4aa**).

continued with stirring at 90 °C for 10 h, and the reaction did not proceed indicating that no catalytically active Cu remained in the filtrate. The filtrate was analyzed from ICP-AES to study the presence of copper at the ppm level, but we did not observe any Cu content in it. The hot filtration test and ICP-AES analysis results revealed that there was no leaching of CuI NPs from the CSP support.

■ CONCLUSION

In summary, we have developed a facile and green protocol for one-pot synthesis of aminoindolizines and chalcones from the same reactants with anomalous selectivity dependent on secondary amines and solvents. Ethylene glycol was the best recyclable solvent to afford the aminoindolizines exclusively from wide range of substrates. However, the selectivity in the product formation depends on the secondary amines used in the reaction under solvent free conditions. Heterocyclic chalcones with *E*-stereochemistry were obtained in excellent yield in the presence of 3-methylpiperidine, piperidine, pyrrolidine, and piperazine. The present protocol follows green and sustainable principles with higher atom economy (94%), and a smaller *E*-factor (0.06). Moreover, the CuI/CSP catalyst was recycled for five times without significant loss in its catalytic activity.

■ EXPERIMENTAL SECTION

Typical Procedure for Synthesis of CuI/CSP Composites. Glucose (6 g) was dissolved in distilled water (60 mL), and the resulted clear solution was added to 600 mg of Ph_3P in a Teflon container of 100 mL capacity in stainless steel autoclave. The reaction was maintained at 180 °C for 6 h, and then cooled to room temperature. The dark precipitate of carbon spheres was collected by centrifugation and washed several times with ethanol. The carbon spheres were dried in a vacuum oven at 80 °C for 6 h. The freshly prepared carbon spheres (200 mg) and CuI (200 mg) were mixed in a 100 mL round-bottomed flask containing 40 mL of ethanol. The reaction mixture was sonicated for 60 min and followed by reflux at 90 °C for 2 h. The resulting CuI/carbon sphere (CuI/CSP) composites were collected by centrifugation and were dried at 80 °C under vacuum.

General Procedure for Synthesis of Aminoindolizines (4) and Chalcones (5). A mixture of pyridine-2-carboxaldehye **1** (1 mmol), secondary amines **2** (1 mmol), phenylacetylenes **3** (1 mmol), and CuI/CSP catalyst (5 mg) was stirred at 60 °C in ethylene glycol (2 mL) or solvent free conditions until the reaction was completed as monitored by TLC. After completion of the reaction, ethanol was added to the mixture and the catalyst was separated from the organic layer by centrifugation. The recovered catalyst was washed with ethanol for 3−4 times to remove all adsorbed organic substrates from its surface and dried at 80 °C in a vacuum oven to reuse it in further cycles. The organic layer was evaporated, and the crude products were purified by flash chromatography.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acssuschemeng.5b00701.

> Characterization of recycled CuI/CSP composites such as PXRD, SEM, TEM, and XPS of fresh and recycled catalyst, green metric calculations; ^{1}H NMR, ^{19}F NMR, and ^{13}C NMR spectral data and spectra of all compounds (PDF).

■ AUTHOR INFORMATION

Corresponding Author

*D. S. Rawat. Fax: 91-11-27667501. Tel: 91-11-27662683. E-mail: dsrawat@chemistry.du.ac.in.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

D.S.R. thanks DU-DST PURSE grant and University of Delhi, Delhi, India for financial support. U.C.R. thanks University Grants Commission (UGC) for the award of a senior research fellowship (SRF). We thank USIC−CIF, University of Delhi, for assisting to acquire analytical data.

■ REFERENCES

(1) Sun, X.; Li, Y. Colloidal carbon spheres and their core/shell structures with noble-metal nanoparticles. *Angew. Chem., Int. Ed.* **2004**, *43*, 597−601.

(2) Nieto-Marquez, A.; Romero, R.; Romero, A.; Valverde, J. L. Carbon nanospheres: Synthesis, physicochemical properties and applications. *J. Mater. Chem.* **2011**, *21*, 1664−1672.

(3) Deshmukh, A. A.; Mhlanga, S. D.; Coville, N. J. Carbon spheres. *Mater. Sci. Eng., R* **2010**, *70*, 1−28.

(4) Sun, X.; Li, Y. Hollow carbonaceous capsules from glucose solution. *J. Colloid Interface Sci.* **2005**, *291*, 7−12.

(5) Li, M.; Wu, Q.; Wen, M. A novel route for preparation of hollow carbon nanospheres without introducing template. *Nanoscale Res. Lett.* **2009**, *4*, 1365−1370.

(6) Li, M.; Li, W.; Liu, S. Hydrothermal synthesis, characterization and KOH activation of carbon spheres from glucose. *Carbohydr. Res.* **2011**, *346*, 999−1004.

(7) Titirici, M. M.; Antonietti, M. Chemistry and materials options of sustainable carbon materials made by hydrothermal carbonization. *Chem. Soc. Rev.* **2010**, *39*, 103−116.

(8) Tang, S.; Vongehr, S.; Meng, X. Carbon spheres with controllable silver nanoparticle doping. *J. Phys. Chem. C* **2010**, *114*, 977−982.

(9) Tang, S.; Vongehr, S.; Meng, X. Controllable incorporation of Ag and Ag−Au nanoparticles in carbon spheres for tunable optical and catalytic properties. *J. Mater. Chem.* **2010**, *20*, 5436−5445.

(10) Yang, Q.; Zhang, J.; Zhang, L.; Fu, H.; Zheng, X.; Yuan, M.; Chen, H.; Li, R. Ruthenium nanoparticles on colloidal carbon spheres: An efficient catalyst for hydrogenation of ethyl lactate in aqueous phase. *Catal. Commun.* **2013**, *40*, 37−41.

(11) Xu, C.; Cheng, L.; Shen, P.; Liu, Y. Methanol and ethanol electro-oxidation on Pt and Pd supported on carbon microspheres in alkaline media. *Electrochem. Commun.* **2007**, *9*, 997−1001.

(12) Kamal, A.; Srinivasulu, V.; Seshadri, B. N.; Markandeya, N.; Alarifi, A.; Shankaraiah, N. Water mediated Heck and Ullmann couplings by supported palladium nanoparticles: Importance of surface polarity of the carbon spheres. *Green Chem.* **2012**, *14*, 2513−2522.

(13) Putta, C. B.; Ghosh, S. Palladium nanoparticles on amphiphilic carbon spheres: A green catalyst for Suzuki−Miyaura reaction. *Adv. Synth. Catal.* **2011**, *353*, 1889−1896.

(14) Makowski, P.; Cakan, R. D.; Antonietti, M.; Goettmann, F.; Titirici, M. M. Selective partial hydrogenation of hydroxy aromatic derivatives with palladium nanoparticles supported on hydrophilic carbon. *Chem. Commun.* **2008**, 999−1001.

(15) Qian, Y.; Lu, S.; Gao, F. Synthesis of copper nanoparticles/carbon spheres and application as a surface-enhanced Raman scattering substrate. *Mater. Lett.* **2012**, *81*, 219−221.

(16) Xu, Y.; Jian, G.; Zachariah, M. R.; Wang, C. Nano-structured carbon-coated CuO hollow spheres as stable and high rate anodes for lithium-ion batteries. *J. Mater. Chem. A* **2013**, *1*, 15486−15490.

(17) Jia, B.; Qin, M.; Zhang, Z.; Chu, A.; Zhang, L.; Liu, Y.; Lu, H.; Qu, X. One-pot synthesis of Cu−carbon hybrid hollow spheres. *Carbon* **2013**, *62*, 472−480.

(18) Cheng, Y.; Niu, X.; Zhao, T.; Yuan, F.; Zhu, Y.; Fu, H. Hydrothermal synthesis of Cu@C composite spheres by one-step method and their use as sacrificial templates to synthesize a CuO@SiO_2 core−shell structure. *Eur. J. Inorg. Chem.* **2013**, 4988−4997.

(19) Allen, S. E.; Walvoord, R. R.; Padilla-Salinas, R.; Kozlowski, M. C. Aerobic copper-catalyzed organic reactions. *Chem. Rev.* **2013**, *113*, 6234−6458.

(20) Decan, M. R.; Impellizzeri, S.; Marin, M. L.; Scaiano, J. C. Copper nanoparticle heterogeneous catalytic 'click' cycloaddition confirmed by single-molecule spectroscopy. *Nat. Commun.* **2014**, *5*, 4612.

(21) Rotstein, B. H.; Zaretsky, S.; Rai, V.; Yudin, A. K. Small heterocycles in multicomponent reactions. *Chem. Rev.* **2014**, *114*, 8323−8359.

(22) Sharma, V.; Kumar, V. Indolizine: A biologically active moiety. *Med. Chem. Res.* **2014**, *23*, 3593−3606.

(23) Liu, R.-R.; Cai, Z.-Y.; Lu, C.-J.; Ye, S.-C.; Xiang, B.; Gao, J.; Jia, Yi-X. Indolizine synthesis *via* Cu-catalyzed cyclization of 2-(2-enynyl)pyridines with nucleophiles. *Org. Chem. Front.* **2015**, *2*, 226−230.

(24) Xiang, L.; Yang, Y.; Zhou, X.; Liu, X.; Li, X.; Kang, X.; Yan, R.; Huang, G. I_2-Mediated oxidative cyclization for synthesis of substituted indolizines. *J. Org. Chem.* **2014**, *79*, 10641−10647.

(25) Kucukdisli, M.; Opatz, T. One-pot synthesis of polysubstituted indolizines by an addition/cycloaromatization sequence. *J. Org. Chem.* **2013**, *78*, 6670−6676.

(26) Yang, Y.; Xie, C.; Xie, Y.; Zhang, Y. Synthesis of functionalized indolizines *via* copper-catalyzed annulation of 2-alkylazaarenes with *α,β*-unsaturated carboxylic acids. *Org. Lett.* **2012**, *14*, 957−959.

(27) Barluenga, J.; Lonzi, G.; Riesgo, L.; Lopez, L. A.; Tomás, M. Pyridine activation *via* copper(I)-catalyzed annulation toward indolizines. *J. Am. Chem. Soc.* **2010**, *132*, 13200−13202.

(28) Albaladejo, M. J.; Alonso, F.; González-Soria, M. J. Synthetic and mechanistic studies on the solvent-dependent copper-catalyzed formation of indolizines and chalcones. *ACS Catal.* **2015**, *5*, 3446−3456.

(29) Mishra, S.; Bagdi, A. K.; Ghosh, M.; Sinha, S.; Hajra, A. Zinc iodide: A mild and efficient catalyst for one-pot synthesis of aminoindolizines *via* sequential A3 coupling/cycloisomerization. *RSC Adv.* **2014**, *4*, 6672−6676.

(30) Albaladejo, M. J.; Alonso, F.; Yus, M. Synthesis of indolizines and heterocyclic chalcones catalyzed by supported copper nanoparticles. *Chem. - Eur. J.* **2013**, *19*, 5242−5245.

(31) Mishra, S.; Naskar, B.; Ghosh, R. CuCl catalyzed green and efficient one-pot synthesis of aminoindolizine frameworks *via* three-component reactions of aldehydes, secondary amines, and terminal alkynes in PEG. *Tetrahedron Lett.* **2012**, *53*, 5483−5487.

(32) Dighe, S. U.; Hutait, S.; Batra, S. Copper-catalyzed multicomponent coupling/cycloisomerization reaction between substituted 1-formyl-9*H*-*β*-carbolines, secondary amines, and substituted alkynes for the synthesis of substituted 3-aminoindolizino[8,7-b]indoles. *ACS Comb. Sci.* **2012**, *14*, 665−672.

(33) Patil, S.; Patil, S. V.; Bobade, V. D. Synthesis of aminoindolizine and quinoline derivatives *via* $Fe(acac)_3$/TBAOH-catalyzed sequential cross-coupling−cycloisomerization reactions. *Synlett* **2011**, *2011*, 2379−2383.

(34) Bai, Y.; Zeng, J.; Ma, J.; Gorityala, B. K.; Liu, X.-W. Quick access to druglike heterocycles: Facile silver-catalyzed one-pot multicomponent synthesis of aminoindolizines. *J. Comb. Chem.* **2010**, *12*, 696−699.

(35) Yan, B.; Liu, Y. Gold-catalyzed multicomponent synthesis of aminoindolizines from aldehydes, amines, and alkynes under solvent-free conditions or in water. *Org. Lett.* **2007**, *9*, 4323−4326.

(36) Rajesh, U. C.; Pavan, V. S.; Rawat, D. S. Hydromagnesite rectangular thin sheets as efficient heterogeneous catalysts for the synthesis of 3-substituted indoles *via* Yonemitsu-type condensation in water. *ACS Sustainable Chem. Eng.* **2015**, *3*, 1536−1543.

(37) Rajesh, U. C.; Wang, J.; Prescott, S.; Tsuzuki, T.; Rawat, D. S. RGO/ZnO nanocomposite: An efficient, sustainable, heterogeneous, amphiphilic catalyst for synthesis of 3-substituted indoles in water. *ACS Sustainable Chem. Eng.* **2015**, *3*, 9−18.

(38) Rajesh, U. C.; Kholiya, R.; Thakur, A.; Rawat, D. S. [TBA][Gly] Ionic liquid promoted multi-component synthesis of 3-substituted indoles and indolyl-4*H*-chromenes. *Tetrahedron Lett.* **2015**, *56*, 1790−1793.

(39) Rajesh, U. C.; Divya; Rawat, D. S. Functionalized superparamagnetic Fe_3O_4 as an efficient quasi-homogeneous catalyst for multicomponent reactions. *RSC Adv.* **2014**, *4*, 41323−41330.

(40) Rajesh, U. C.; Kholiya, R.; Pavan, V. S.; Rawat, D. S. Catalyst-free, ethylene glycol promoted one-pot three component synthesis of 3-amino alkylated indoles *via* Mannich-type reaction. *Tetrahedron Lett.* **2014**, *55*, 2977−2981.

(41) Rajesh, U. C.; Manohar, S.; Rawat, D. S. Hydromagnesite as an efficient recyclable heterogeneous solid base catalyst for the synthesis of flavanones, flavonols and 1,4-dihydropyridines in water. *Adv. Synth. Catal.* **2013**, *355*, 3170−3178.

(42) Thakur, A.; Tripathi, M.; Rajesh, U. C.; Rawat, D. S. Ethylenediammonium diformate (EDDF) in PEG600: an efficient ambiphilic novel catalytic system for the one-pot synthesis of 4*H*-pyrans *via* Knoevenagel condensation. *RSC Adv.* **2013**, *3*, 18142−18148.

(43) Arya, K.; Rajesh, U. C.; Rawat, D. S. Proline confined FAU zeolite: Heterogeneous hybrid catalyst for the synthesis of spiroheterocycles *via* a Mannich type reaction. *Green Chem.* **2012**, *14*, 3344−3351.

(44) Arya, K.; Rawat, D. S.; Sasai, H. Zeolite supported Bronsted-acid ionic liquids: An eco approach for synthesis of spiro[indole-pyrido[3,2-e]thiazine] in water under ultrasonication. *Green Chem.* **2012**, *14*, 1956−1963.

(45) Yang, M.; Xu, J.; Xu, S.; Zhu, J.; Chen, H. Preparation of porous spherical CuI nanoparticles. *Inorg. Chem. Commun.* **2004**, *7*, 628−630.

(46) Jin, Y. Z.; Gao, C.; Hsu, W. K.; Zhu, Y.; Huczko, A.; Bystrzejewski, M.; Roe, M.; Lee, C. Y.; Acquah, S.; Kroto, H.; Walton, D. R. M. Large-scale synthesis and characterization of carbon spheres prepared by direct pyrolysis of hydrocarbons. *Carbon* **2005**, *43*, 1944−1953.