Journal of Catalysis 337 (2016) 167-176

Contents lists available at ScienceDirect

Journal of Catalysis

journal homepage: www.elsevier.com/locate/jcat

Synthesis of indolizines through aldehyde-amine-alkyne couplings using metal-organic framework Cu-MOF-74 as an efficient heterogeneous catalyst

Giao H. Dang, Huy Q. Lam, Anh T. Nguyen, Dung T. Le, Thanh Truong^{*}, Nam T.S. Phan^{*} Department of Chemical Engineering, HCMC University of Technology, VNU-HCM, 268 Ly Thuong Kiet, District 10, Ho Chi Minh City, Viet Nam



A crystalline copper-based metal-organic framework Cu-MOF-74 was synthesized, and was characterized by X-ray powder diffraction (XRD), scanning electron microscopy (SEM), transmission electron microscopy (TEM), thermogravimetric analysis (TGA), Fourier transform infrared (FT-IR), atomic absorption spectrophotometry (AAS), and nitrogen physisorption measurements. The Cu-MOF-74 exhibited high catalytic activity in the synthesis of indolizines through aldehyde–amine–alkyne three-component coupling transformation and higher than those of other Cu-MOFs such as Cu₂(BDC)₂(DABCO), Cu₃(BTC)₂, Cu(BDC), Cu₂(NDC)₂(DABCO), and Cu₄I₄(DABCO)₂. The reactions could only proceed to produce indolizines in the presence of the solid Cu-MOF catalyst, and contribution from active copper species leached from the solid Cu-MOF-74, if any, was negligible. The Cu-MOF catalyst be recovered and reused several times for the synthesis of indolizines without a significant degradation in catalytic activity. To the best of our knowledge, the synthesis of indolizines using a recyclable heterogeneous catalyst was not previously mentioned in the literature.

© 2016 Elsevier Inc. All rights reserved.

1. Introduction

ARTICLE INFO

Received 1 December 2015

Revised 9 February 2016

Accepted 9 February 2016

Metal-organic framework

Heterogeneous catalyst

Article history

Keywords:

Indolizines

Cu-MOF-74

Coupling

Indolizines have attracted significant attention as important scaffolds found in many bioactive natural products, pharmaceuticals, and agrochemicals, and as versatile intermediates in a variety of organic transformations [1–5]. As a result, several synthesis approaches have been developed for the construction of these *N*-fused heterocycles [6]. One of the most popular methods should be the 1,3-dipolar cycloaddition of electron deficient alkenes or alkynes with pyridinium ylides in the presence of a base and an oxidant [5,7,8]. However, the problem of using the excess amounts of the base and the oxidant for the transformation still remains to be solved [5]. Huang and co-workers previously reported the synthesis of substituted indolizines by means of I2-mediated oxidative tandem cyclization between various substituted aromatic/aliphatic enolizable aldehydes and 2-pyridylacetates/acetonitrile/acetone [2]. Catalytic transformations with different transition metals have recently been investigated for the synthesis of indolizines. Zhang and co-workers pointed out that arylated indolizines could be produced by the Cu(OAc)₂-catalyzed annulation of 2-alkylazaarenes with α,β -unsaturated carboxylic acids [9]. Gevorgyan and co-workers developed the Cu(MeCN)₄PF₆-catalyzed denitrogenative transannulation reaction of pyridotriazoles with terminal alkynes en route to indolizines [10]. Moreover, these *N*-fused heterocycles could also be formed via homogeneous palladium-[11–13], silver- [14,15], gold- [16], and samarium-catalyzed [17] transformations. Recently, González-Soria and co-workers reported the first example of heterogeneous catalytic synthesis of indolizines through aldehyde–amine–alkyne coupling using copper nanoparticles supported on activated carbon as catalyst [18]. Unfortunately, this solid catalyst could not be recycled and reused in the synthesis of indolizines, though the same catalyst could be reutilized in the synthesis of chalcones [18]. Metal-organic frameworks (MOFs), also known as porous coor-

Metal-organic frameworks (MOFs), also known as porous coordination polymers, have emerged as a new family of crystalline materials composed of organic linkers that connect metal ions or metal clusters to produce one-, two-, or three-dimensional networks [19–24]. A large number of MOFs could be formed by linking numerous organic bridging ligands with several metal cations of diverse oxidation states and coordination geometries [25], offering several advantages such as structural diversity, well-defined structures, high surface areas, high porosity, and the ability to modify the surface hydrophobicity/hydrophilicity [19–24,26–29]. With these special properties, potential applications of MOFs in many fields have been extensively explored during the last decade [19,20,30–35]. MOFs as heterogeneous catalysts have attracted







^{*} Corresponding authors. Fax: +84 8 38637504.

E-mail addresses: tvthanh@hcmut.edu.vn (T. Truong), ptsnam@hcmut.edu.vn (N.T.S. Phan).

immense worldwide interests from both industry and academia [36–38]. All metal cations or functional groups on the organic bridging ligands in MOF structure could be useful for catalytic reactions; therefore, the dispersion and the loading of active sites on the solid framework could be maximized [37,39–45]. During the last few years, many MOF-catalyzed organic reactions have been reported in the literature [36-38,46,47], ranging from both carbon-carbon [48-58] to carbon-heteroatom forming [59-67] transformations. Among a variety of popular MOFs, copper-based frameworks have been explored as catalysts for numerous organic transformations due to their unsaturated open copper metal sites [58,62,68-74]. In this work, we wish to report the synthesis of indolizines through aldehyde-amine-alkyne three-component coupling using a copper-based metal-organic framework Cu-MOF-74 as an efficient heterogeneous catalyst. The solid catalyst could be recycled and reused many times for the transformation without a significant degradation in catalytic activity. To the best of our knowledge, the synthesis of indolizines using a recyclable heterogeneous catalyst was not previously mentioned in the literature.

2. Experimental

2.1. Materials and instrumentation

All reagents and starting materials were obtained commercially from Sigma-Aldrich and Merck, and were used as received without any further purification unless otherwise noted. Nitrogen physisorption measurements were conducted using a Micromeritics 2020 volumetric adsorption analyzer system. Samples were pretreated by heating under vacuum at 150 °C for 3 h. A Netzsch Thermoanalyzer STA 409 was used for thermogravimetric analysis (TGA) with a heating rate of 10 °C/min under a nitrogen atmosphere. X-ray powder diffraction (XRD) patterns were recorded using a Cu Ka radiation source on a D8 Advance Bruker powder diffractometer. Scanning electron microscopy studies were conducted on a S4800 Scanning Electron Microscope (SEM). Transmission electron microscopy studies were performed using a JEOL JEM 1400 Transmission Electron Microscope (TEM) at 80 kV. The Cu-MOF-74 sample was dispersed on holey carbon grids for TEM observation. Elemental analysis with atomic absorption spectrophotometry (AAS) was performed on an AA-6800 Shimadzu. Fourier transform infrared (FT-IR) spectra were obtained on a Nicolet 6700 instrument, with samples being dispersed on potassium bromide pallets.

Gas chromatographic (GC) analyses were performed using a Shimadzu GC 2010-Plus equipped with a flame ionization detector (FID) and an SPB-5 column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25μ m). The temperature program for GC analysis held samples at 100 °C for 1 min, heated them from 100 to 280 °C at 40 °C/min, and held them at 280 °C for 6.5 min. Inlet and detector temperatures were set constant at 280 °C. Diphenyl ether was used as an internal standard to calculate GC yield. GC-MS analyses were performed using a Shimadzu GCMS-QP2010Ultra with a ZB-5MS column (length = 30 m, inner diameter = 0.25 mm, and film thickness = 0.25 μ m). The temperature program for GC-MS analysis held samples at 50 °C for 2 min, heated samples from 50 to 280 °C at 10 °C/min and held them at 280 °C for 10 min. Inlet temperature was set constant at 280 °C. MS spectra were compared with the spectra gathered in the NIST library. The ¹H NMR and ¹³C NMR were recorded on Bruker AV 500 spectrometers using residual solvent peak as a reference.

2.2. Synthesis of the metal-organic framework Cu-MOF-74

In a typical preparation, a solid mixture of H_2 dhtp (H_2 dhtp = 2,5-dihydroxyterephthalic acid; 0.495 g, 2.5 mmol), and

Cu(NO₃)₂·3H₂O (1.21 g, 5 mmol) was dissolved in a mixture of DMF (DMF = *N*,*N'*-dimethylformamide; 47 mL), and 2-propanol (3 mL). The resulting solution was then distributed to seven 10 mL vials. The vials were heated at 85 °C in an isothermal oven for 18 h. After cooling the vials to room temperature, the solid product was removed by decanting with mother liquor and washed in DMF (3×20 mL). Solvent exchange was carried out with 2-propanol (3×20 mL) at room temperature. The material was then evacuated under vacuum at 150 °C for 5 h, yielding 0.50 g of Cu-MOF-74, Cu₂(DOBDC), in the form of reddish black crystals (62% yield based on H₂dhtp).

2.3. Catalytic studies

In a typical experiment, a mixture of 2-pyridincarboxaldehyde (0.190 mL, 2.0 mmol), piperidine (0.100 mL, 1.0 mmol), phenylacetylene (0.165 mL, 1.5 mmol) and diphenyl ether (0.156 mL, 1 mmol) as an internal standard in *n*-butanol (2 mL) was added into a 10 mL vial containing the pre-determining amount of Cu-MOF-74 catalyst. The catalyst amount (in mol% and wt.%) was calculated with respect to the copper/piperidine molar ratio (weight was corrected by adsorbed solvent as seen by TGA). The reaction mixture was stirred at 100 °C under argon for 5 h. GC yield was monitored by withdrawing aliquots from the reaction mixture at different time intervals, quenching with water (1 mL). The organic components were then extracted into ethyl acetate (4 mL), dried over anhydrous Na₂SO₄, and analyzed by GC with reference to diphenyl ether. The combined organic layers were concentrated under reduced pressure. The resulting residue was purified by column chromatography (ethyl acetate/hexane = 1:9) to afford 3-phe nyl-1-(piperidin-1-yl)indolizine. The product identity was further confirmed by GC-MS, ¹H NMR and ¹³C NMR. To investigate the recyclability of Cu-MOF-74, the catalyst was separated from the reaction mixture by simple centrifugation, washed with copious amounts of DMF and 2-propanol, dried 150 °C under vacuum in 2 h, and reused if necessary. For the leaching test, a catalytic reaction was stopped after 1 h, analyzed by GC, and centrifuged to remove the solid catalyst. The reaction solution was then stirred for a further 5 h. Reaction progress, if any, was monitored by GC as previously described.

3. Results and discussion

The metal-organic framework Cu-MOF-74 was synthesized in a yield of 62% by solvothermal method according to a slightly modified literature procedure [75], and was characterized by a variety of different techniques, including XRD, SEM, TEM, TGA, FT-IR, AAS, and nitrogen physisorption measurements (Figs. S1–S7). The analysis results were in agreement with previous studies [75]. These confirmed that the synthesized Cu-MOF-74 possesses paddle wheel structure, open metal sites, high coordinate metal ion, and exceptionally large pore apertures. In particular, powder X-ray diffraction pattern showed the typical reflections of MOF-74 phase. The permanent micro-porosity with Brunauer-Emmett-Teller specific surface area of 1101 m²/g, a pore volume of $0.50 \text{ cm}^3/\text{g}$ and an average pore diameter of about 13 Å was confirmed by the basically type-1 adsorption/desorption isotherm. Scanning electron microscopy analysis showed the homogeneity with respect to needle-shaped crystals. Thermal gravimetric analysis (TGA) of activated Cu-MOF-74 shows high thermal stability (>300 °C) and the measured mass percent of residue CuO is consistent with the EA data. AAS provided 36.51% copper content which is close to the calculated value of 37.72%. Finally, FT-IR spectra of Cu-MOF-74 indicated the presence of bonded carboxylate organic linkers.

The Cu-MOF-74 was used as a heterogeneous catalyst for the three-component coupling reaction of 2-pyridincarboxaldehyde, piperidine, and phenylacetylene to form 3-phenyl-1-(piperidin-1yl)indolizine as the principal product (Scheme 1). The reaction selectivity was calculated with regard to detectable by-products including homo-coupling of phenyl acetylene and the addition of acetylide to aldehyde forming chalcone-type products. Initial studies addressed the effect of temperature (Fig. 1). The threecomponent coupling reaction was carried out in *n*-butanol under argon for 5 h, using 2-pyridincarboxaldehyde:piperidine:phenyla cetylene molar ratio of 2:1:1.5, at piperidine concentration of 0.5 M, in the presence of 5 mol% (3.74 wt.%) of Cu-MOF-74 catalyst. It was observed that no desired product was detected for the reaction carried out at room temperature. The transformation proceeded with difficulty at 80 °C, though 41% yield was observed at 80 °C. This value could be improved to 45% at 90 °C. Increasing the reaction temperature to 100 °C led to a significant enhancement in the reaction yield. Indeed, up to 74% yield was achieved for the reaction carried out at 100 °C. Performing the threecomponent coupling reaction at higher temperature than 100 °C was found to be unnecessary as the formation of (A) was not improved significantly.

When organic transformations were carried out in the presence of solid catalysts, the solvent could exhibit a significant effect on the reaction rate, depending on the nature of the catalyst [76,77]. In the first example of the heterogeneous catalytic aldehyde-ami ne-alkyne coupling using copper nanoparticles supported on activated carbon as catalyst, González-Soria and co-workers reported that indolizines were produced in dichloromethane as solvent, while chalcones were formed under solvent-free condition [18]. It was therefore decided to investigate the impact of different solvents (Fig. 2). The three-component coupling reaction was carried out at 100 °C under argon for 5 h, using 2-pyridincarboxaldehyde: piperidine:phenylacetylene molar ratio of 2:1:1.5, at piperidine concentration of 0.5 M, in the presence of 5 mol% Cu-MOF-74 catalvst, in *n*-butanol, dichloroethane, dimethyl sulfoxide (DMSO), acetonitrile, N-methyl-2-pyrrolidone (NMP), dimethylformamide (DMF), dimethylacetamide (DMA), diethylformamide (DEF), toluene, p-xylene, 1,4-dioxane, and diglyme as solvent, respectively. In contrast to previous studies in solvent-dependence on the same reaction, neither indolizines nor chalcones were produced in the absence of solvent, indicating the necessity of solvent for the formation of desired product (A) [18]. DMA, DEF, toluene, pxylene, 1,4-dioxane, and diglyme were found to be unsuitable as solvent for the three-component coupling reaction using Cu-MOF-74 catalyst. Acetonitrile, NMP, and DMF exhibited better performance, affording 22% yield. This value could be improved to 29% for the case of DMSO. Dichloroethane was more suitable for the transformation than DMSO. n-Butanol was found to be the solvent of choice, with 74% yield of 3-phenyl-1-(piperidin-1-yl)indolizine being achieved.

Another factor should be addressed for the three-component coupling reaction of 2-pyridincarboxaldehyde, piperidine, and



Fig. 1. Effect of temperature on the reaction yield.



Fig. 2. Effect of solvent on the reaction yield.

phenylacetylene. The three-component coupling reaction was carried out in *n*-butanol at 100 °C under argon for 5 h, at piperidine concentration of 0.5 M, in the presence of 5 mol% Cu-MOF-74 catalyst, at various ratios (Fig. 3). It was found that the reactant molar ratio exhibited a significant impact on reaction efficiency. Using 1 equivalent of pyridincarboxaldehyde and 1 equivalent of phenylacetylene, the reaction proceeded with difficulty, affording only 21% yield. Experimental results indicated that when less than 2 equivalents of pyridincarboxaldehyde was employed, the yield of (**A**) was not improved significantly by increasing the amount of phenylacetylene. Indeed, only 36% yield was detected for the reaction using 2-pyridincarboxaldehyde:piperidine:phenylacetylene molar ratio of 1.5:1:1.5. However, when more than 2 equivalents



desired products

Detectable byproducts





Fig. 3. Effect of 2-pyridincarboxaldehyde:piperidine:phenylacetylene molar ratio on the reaction yield.

of pyridincarboxaldehyde were used, the formation of (**A**) was dramatically enhanced by increasing the amount of phenylacetylene. The reaction yield could be improved to 86% for the reaction using 2-pyridincarboxaldehyde:piperidine:phenylacetylene molar ratio of 2.5:1:1.5. It was observed that changing this reactant molar ratio led to a drop in the reaction yield.

The possibility that some of catalytically active sites on the solid catalyst could dissolve into the liquid phase during the course of the reaction should be examined for liquid phase organic transformations [77]. In order to determine whether active copper species dissolved from the solid Cu-MOF-74 catalyst contributed to the formation of desired product (A), a control experiment was carried out (Fig. 4). Apparently, if (A) was still formed after the solid Cu-MOF-74 catalyst was removed from the mixture, this behavior would indicate that the three-component coupling reaction would not proceed under real heterogeneous catalysis conditions. The liquid phase was separated from the solid Cu-MOF-74 after 1 h reaction time by centrifugation. The reaction solution was then transferred to a new reactor vessel, and stirred for an additional 5 h at 100 °C under argon with aliquots being sampled at different time intervals, and analyzed by GC. It was found that no further product (A) was produced in the absence of the solid Cu-MOF-74 catalyst. Additionally, the content of Cu species in reaction filtrate was also measured using AAS. The results indicated that amount of Cu in reaction filtrate and pure reaction solvents were similar with less than 1 ppm of Cu was detected. These observations would confirm that the three-component coupling reaction could only proceed in the presence of the solid Cu-MOF-74 catalyst, and there was no contribution from leached active copper species in the solution.

To further address the issue of where the catalysis occurs, experiments using grinded Cu-MOF-74 were conducted under identical conditions (Fig. 5). It was observed that similar reaction conversions were obtained during the reaction course in both cases. In addition, the cavity size according to the Cu-MOF-74 structure is about 12–14 Å while the kinetic diameters of aromatic reactant and product are calculated to be 6 Å and 12 Å, respectively [78,79]. Furthermore, pore flexibility in MOFs upon temperature and guest molecules has been previously reported [80]. Though it is likely that reactions take place inside the catalyst pores, further spectroscopic studies are still needed.

To gain insights into the reaction pathway, several mechanistic studies were carried out. In the first experiment, the reaction was carried out in *n*-butanol at 100 °C under argon, using 2-pyridincar boxaldehyde:piperidine:phenylacetylene molar ratio of 2.5:1:1.5, at piperidine concentration of 0.5 M, in the presence of 5 mol% Cu-MOF-74 catalyst. After 1 h reaction time with 52% yield of (A) being obtained, argon was removed and replaced by air, and the reaction mixture was heated under air at 100 °C for further 5 h. It was found that 65% yield was detected under this condition. It should be noted that the transformation carried out under argon could proceed to 86% yield. Moreover, 11% of by-product (B) and (C) was observed in the product mixture for the reaction under air, while only 4% of (**B**) and (**C**) was detected for that under argon. In the second experiment, the reaction was carried out under argon in the presence of water (5% by volume) and only 54% yield of (A) in conjunction with 12% of alkyne dimerization product (C) was detected in the product mixture. These observations suggested that the formation of (A) was not favored by air or by water residue in the solvent. In the third experiment, the Cu-MOF-74 catalyst was soaked in pyridine as catalyst poison prior to use. It was also found that the Cu-MOF catalyst was significantly deactivated by pyridine under this condition, with only 18% yield of principal product being detected. It could be proposed that the strong adsorption of pyridine on the copper sites in the Cu-MOF-74 deactivated the catalyst, confirming the role of copper sites in the transformation. However, further mechanistic studies would be necessary to elucidate the reaction pathway of the threecomponent coupling reaction using Cu-MOF-74 catalyst.

With these results in mind, we then decided to investigate the effect of catalyst concentration (Fig. 6). The three-component coupling reaction was carried out in *n*-butanol at 100 °C under argon for 5 h, using 2-pyridincarboxaldehyde:piperidine:phenylacety



Fig. 4. Leaching test indicated no contribution from homogeneous catalysis of leached species.



Fig. 5. Reactions with grinded Cu-MOF-74.

lene molar ratio of 2.5:1:1.5, at piperidine concentration of 0.5 M, in the presence of 0.5 mol%, 1 mol%, 3 mol%, 5 mol%, and 7 mol% Cu-MOF-74 catalyst, respectively. It should be noted that no product was detected in the absence of the Cu-MOF-74 catalyst. As mentioned earlier, the reaction using 5 mol% catalyst afforded 86% yield. Interestingly, it was found that increasing the catalyst concentration to 7 mol% resulted in a significant drop in the reaction yield. Decreasing the catalyst concentration from 5 mol% to 3 mol% led to 88% yield, while up to 99% yield of this product was achieved for the reaction using 1 mol% catalyst. Using lower than 1 mol% catalyst led to a slight decrease in the reaction yield. Repeated experiments gave similar results. The explanation for this phenomenon might come from the cooperative and synergistic effects of poly-Cu nuclear in reaction mixture facilitating the by-product formation routes at high copper concentrations [81].

For liquid phase organic reactions using solid catalysts, the reactant concentration would exhibit a significant effect on the reaction rate due to the mass transfer phenomenon. It was therefore decided to explore the impact of reactant concentration on the reaction yield (Fig. 7). The coupling reaction was carried out in *n*-butanol at 100 °C under argon for 5 h, using 2-pyridincarboxal dehyde:piperidine:phenylacetylene molar ratio of 2.5:1:1.5, in the presence of 5 mol% Cu-MOF-74 catalyst, at different piperidine concentrations. It was found that the reactant concentration also exhibited a significant impact on the three-component coupling reaction, and optimal GC yield was observed at piperidine concentration of 0.67 M.

The catalytic activity of Cu-MOF-74 in the three-component coupling reaction of 2-pyridincarboxaldehyde, piperidine, and phenylacetylene was also compared with that of other homogeneous catalysts (Table 1). It was observed that the reaction using CuF₂ catalyst proceeded with difficulty, affording only 39% yield. $Cu(CH_3COO)_2$ was found to be more active than CuF_2 , with 66% vield being detected. Other homogeneous catalysts, including CuBr, CuCl, CuI, CuBr₂, CuCl₂, Cu(NO₃)₂, and Cu(CH₃COCH₂COO)₂ exhibited high activity in the three-component coupling reaction. In particular. (A) was produced in a vield of 96% for the reaction using CuI catalyst, while 98% yield was obtained for that using CuBr, CuBr₂, Cu(NO₃)₂, and Cu(CH₃COCH₂COO)₂. The reaction yield could be improved to 99% when CuCl₂ was used as catalyst. As mentioned earlier, 99% yield was also achieved in the presence of Cu-MOF-74 catalyst. It should be noted that (C) was also detected for the three-component coupling reaction using these catalysts. Indeed, a selectivity of 96% to (A) was observed for the CuCl₂catalyzed transformation, while 97% selectivity was obtained for the case of Cu-MOF-74. It is worth mentioning that as compared to homogeneous counterparts, traditional heterogeneous catalysts often provide lower activity. However, in this report, heteroge-



Fig. 6. Effect of catalyst concentration on the reaction yield.



Fig. 7. Effect of piperidine concentration on the reaction yield.

Table 1

Different homogeneous catalysts for the three-component coupling reaction.

Entry	Туре	Catalyst	GC yield (%)
1		Cu-MOF-74	99
2	Homogeneous copper salts	CuBr	98
3		CuI	96
3		CuBr ₂	98
4		CuCl ₂	99
5		CuF ₂	39
6		Cu(NO ₃)	98
7		$Cu(OAc)_2$	66
8		Cu(CH ₃ COCH ₂ COO) ₂	98
9	Other homogeneous catalysts	MnSO ₄	2
10		Fe(NO ₃) ₃	2
11		Ni(NO ₃) ₂	4
12		CoCl ₂	2
13		ZrCl ₄	2
14		AlCl ₃	2
15		$Zn(NO_3)_2$	3

Coupling reaction was carried out in *n*-butanol at 100 °C under argon for 5 h, using 2-pyridincarboxaldehyde:piperidine:phenylacetylene molar ratio of 2.5:1:1.5, at piperidine concentration of 0.67 M, in the presence of 1 mol% catalyst.

neous Cu-MOF-74 possesses similar or better activity than other tested Cu salts which were frequently used as homogeneous catalysts in typical cross-coupling reactions. To further elucidate the kind of active centers, reactions using other first-row transition metals (entries 9–13) and strong Lewis acids (entries 14, 15) were performed. The catalysis results confirmed the Cu active site for tested reactions with <5% of desired products was observed in other cases.

To highlight the significant point of using Cu-MOF-74 as catalyst, reactions using other heterogeneous catalysts were carried out (Table 2). These catalysts were synthesized by solvothermal method, and characterized according to literature procedures [74,75,90–94]. It was observed that several Cu-MOFs were found to be active for the three-component coupling reaction. Among these Cu-MOFs, Cu-MOF-74 offered the best performance. Cu₄I₄(DABCO)₂ could also be used as catalyst for the threecomponent coupling reaction, producing 90% yield. The reaction using Cu₂(BDC)₂(DABCO) or Cu₃(BTC)₂ as catalyst could proceed to 88% yield, while 84% and 67% yields were detected for the case of Cu(BDC) and Cu₂(NDC)₂(DABCO), respectively. All tested Cu-MOFs contain open metal sites and possess similar surface areas. High reactivity of Cu-MOF-74 could be rationalized by the aperture size and the additional coordination of -OH group in Cu center. In addition, the use of Cu-MF-74 is technically preferred for the synthesis of other product derivatives which often have bulk size. Besides, traditional Cu-ZnO, Cu Y Zeolite, and Cu-ZSM-5 were showed to be inefficient (entries 8-10). As expected from results

Tal	ble	2	
-			

Reaction	using	other	heterogeneous	catalysts.
----------	-------	-------	---------------	------------

Entry	Туре	Catalyst	Reported aperture size (Å)	BET Surface area (m²/g)	GC yield (%)
1	MOFs	Cu-MOF-74	10	1101	99
2		$Cu_4I_4(DABCO)_2$	-	-	90
3		Cu ₂ (BDC) ₂ (DABCO)	7.5	1240 [82]	88
4		Cu ₃ (BTC) ₂	8.0	1250	88
5		Cu(BDC)	5.6	625 [84.85]	84
6		$Cu_2(NDC)_2(DABCO)$	_	-	67
7	Other	CuFe ₂ O ₄			83
	heterogeneous catalysts	2 .			
8	5	Cu-ZnO			25
9		Cu-Y-Zeolite			2
10		Cu-ZSM-5			2
11		Ni-MOF-74	10.3	1126 [86]	3
12		Fe(BDC)	-		3
13		$In_3O(obb)_3(HCO_2)$		1117	3
		(H ₂ O)		[87]	
14		$Zr_4O_4(OH)_4(BDC)_6$	-	(1187) [88]	-
15		Zn-MOF-74	11	496 [89]	-

Coupling reaction was carried out in *n*-butanol at 100 °C under argon for 5 h, using 2-pyridincarboxaldehyde:piperidine:phenylacetylene molar ratio of 2.5:1:1.5, at piperidine concentration of 0.67 M, in the presence of 1 mol% catalyst.







Fig. 9. X-ray powder diffractograms of the fresh (a) and reused (b) Cu-MOF-74 catalyst.



Fig. 10. FT-IR spectra of the fresh (a) and reused (b) Cu-MOF-74 catalyst.

from Table 1, Zn-MOF, Ni-MOF, Fe-MOF, In-MOF, and Zr-MOF exhibited poor activity for the transformation. Mechanistically, studies using Cu-based homogeneous catalysts proposed the necessity of Cu redox center under organometallic viewpoints. These are in good agreement with previous investigation reporting that the saturation of MOFs structure and their oxidation state can be changed during reaction course and maintain the same after completion of reactions [95–97]. In addition, the paddle wheel structure of Cu-MOF-74 is well known to retarding the homocoupling of terminal alkynes which is one of the prominent side reactions in this study [98,99,64].

Although several homogeneous catalysts exhibited high activity, these catalysts could not be recovered and reused. To emphasize the significant point of the Cu-MOF-74 catalyst in this transformation, one issue that should be addressed is the ease of separation as well as the deactivation and reusability of this Cu-MOF catalyst. The Cu-MOF-74 was therefore investigated for recoverability and reusability over 7 successive runs, by repeatedly separating the Cu-MOF catalyst from the reaction mixture, washing it and then reusing it (Fig. 8). The three-component coupling reaction was carried out in n-butanol at 100 °C under argon for 5 h, using 2-pyridincarboxaldehyde:piperidine:phenylacetylene molar ratio of 2.5:1:1.5, at piperidine concentration of 0.67 M, in the presence of 1 mol% Cu-MOF-74 catalyst. Upon completion of the first run, the Cu-MOF catalyst was separated from the reaction mixture by simple centrifugation, washed with copious amounts of DMF and methanol, and dried 150 °C under vacuum in 2 h. The recovered Cu-MOF-74 catalyst was then reused as catalyst in further transformation under identical conditions to those of the first run. Experimental results indicated that the Cu-MOF-74 catalyst could be recovered and reused many times without a significant degradation in catalytic activity. Indeed, the reaction still afforded 96% yield of (A) in the 7th run. Furthermore, the structure of the Cu-MOF-74 catalyst could be maintained during the course of the transformation, as confirmed by XRD (Fig. 9) and FT-IR (Fig. 10) results of the recovered Cu-MOF-74.

The study was then extended to the synthesis of several indolizines using different aldehydes, amines, and alkynes. The reaction was carried out under optimized conditions. The desired indolizine was isolated and purified by column chromatography. It was found that **(A)** was achieved with an isolated yield of 91%. The presence of a substituent on the benzene ring in phenylaceylene led to a drop in the reaction yield. 3-(4-Methoxyphenyl)-1-(piperidin-1-yl)indoli zine was produced in an isolated yield of 78%, while 82% yield of 1-(piperidin-1-yl)-3-*p*-tolylindolizine was obtained for the case of 4-methylphenylacetylene. Changing the alkyne to 4-trifluorome thylphenylacetylene, the reaction afforded 61% yield of 1-(piperidin-1-yl)-3-(4-(trifluoromethyl)phenyl)indolizine. The

Table 3

Three-component synthesis of indolizines using Cu-MOF-74 catalyst.



(continued on next page)

Table 3 (continued)



three-component coupling reaction using 4-bromophenylacetylene produced 3-(4-bromophenyl)-1-(piperidin-1-yl)indolizine in a yield of 88%. Using 1-octyne instead of phenylacetylene, the threecomponent coupling reaction of this alkyne with 2-pyridincarbo xaldehyde and piperidine could proceed to 89% yield of 3-hexyl-1-(piperidin-1-yl)indolizine. Furthermore, using the same protocol, 5 -methyl-3-phenyl-1-(piperidin-1-yl)indolizine, 3-cyclohexyl-1-(pi peridin-1-yl)indolizine, and 1-(4-methylpiperidin-1-yl)-3-phenylin dolizine were produced in a yield of 90%, 90%, and 86%, respectively (Table 3).

4. Conclusions

In summary, the metal-organic framework Cu-MOF-74 was synthesized by a solvothermal method, and was characterized by several techniques including XRD, SEM, TEM, FT-IR, TGA, AAS, and nitrogen physisorption measurements. The Cu-MOF could be used as an efficient heterogeneous catalyst for the synthesis of indolizines through aldehyde-amine-alkyne three-component coupling transformation. High yields to indolizines were achieved in the presence of a catalytic amount of the Cu-MOF (1 mol%). The formation of indolizines was not favored by air or by water residue in the solvent. The Cu-MOF-74 offered higher catalytic activity in the three-component coupling reaction than those of other Cu-MOFs such as Cu₂(BDC)₂(DABCO), Cu₃(BTC)₂, Cu(BDC), Cu₂(NDC)₂ (DABCO), and Cu₄I₄(DABCO)₂. MOFs containing other metal sites such as Ni-MOF-74, Zn-MOF-74, Fe₃O(BDC)₃, In₃O(obb)₃(HCO₂) (H₂O), and Zr₆O₄(OH)₄(BDC)₆ exhibited almost no catalytic activity for the synthesis of indolizines. The aldehyde-amine-alkyne three-component coupling reaction could only proceed to produce

indolizines in the presence of the solid Cu-MOF catalyst, and no contribution from active copper species leached from the solid Cu-MOF-74, if any, was detected. The Cu-MOF catalyst could be separated from the reaction mixture by centrifugation, and could be recovered and reused several times for the synthesis of indolizines without a significant degradation in catalytic activity. The fact that indolizines could be produced via aldehyde–amine–alky ne three-component coupling transformation using a recyclable heterogeneous catalyst should be of significant advantages.

Acknowledgment

The Vietnam National University – Ho Chi Minh City (VNU-HCM) is acknowledged for financial support through Project No. B2015-20-03.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jcat.2016.02.013.

References

- [1] J. Brioche, C. Meyer, J. Cossy, Org. Lett. 17 (2015) 2800-2803.
- [2] L. Xiang, Y. Yang, X. Zhou, X. Liu, X. Li, X. Kang, R. Yan, G. Huang, J. Org. Chem. 79 (2014) 10641–10647.
- [3] J.B. Xia, S.L. You, Org. Lett. 11 (2009) 1187–1190.
- [4] B.V.M. Teodoro, J.T.M. Correia, F. Coelho, J. Org. Chem. 80 (2015) 2529-2538.
- [5] C. Wang, H. Hu, J. Xu, W. Kan, RSC Adv. 5 (2015) 41255-41258.
- [6] L. Xiang, F. Zhang, B. Chen, X. Pang, X. Yang, G. Huang, R. Yan, RSC Adv. 5 (2015) 29424–29427.
- [7] H. Hu, J. Feng, Y. Zhu, N. Gu, Y. Kan, RSC Adv. 2 (2012) 8637–8644.
- [8] A.R. Katritzky, G. Qiu, B. Yang, H.-Y. He, J. Org. Chem. 64 (1999) 7618-7621.
- [9] Y. Yang, C. Xie, Y. Xie, Y. Zhang, Org. Lett. 14 (2012) 957–959.
- [10] V. Helan, A.V. Gulevich, V. Gevorgyan, Chem. Sci. 6 (2015) 1928-1931.
- [11] L. Zhang, X. Li, Y. Liu, D. Zhang, Chem. Commun. 51 (2015) 6333-6336.
- [12] E.J. Choi, S.B. Park, Org. Biomol. Chem. 13 (2015) 5202–5208.
- [13] Z. Li, D. Chernyak, V. Gevorgyan, Org. Lett. 14 (2012) 6056–6059.
- [14] A.N. Pandya, J.T. Fletcher, E.M. Villa, D.K. Agrawal, Tetrahedron Lett. 55 (2014)
- 6922-6924. [15] Y. Bai, J. Zeng, J. Ma, B.K. Gorityala, X.-W. Liu, J. Comb. Chem. 12 (2010) 696-699
- [16] B. Yan, Y. Liu, Org. Lett. 9 (2007) 4323-4326.
- [17] X. Wang, S.-Y. Li, Y.-M. Pan, H.-S. Wang, H. Liang, Z.-F. Chen, X.-H. Qin, Org. Lett. 16 (2014) 580–583.
- [18] M.J. Albaladejo, F. Alonso, M.J. González-Soria, ACS Catal. 5 (2015) 3446-3456.
- [19] H.K. Chae, D.Y. Siberio-Perez, J. Kim, Y. Go, M. Eddaoudi, A.J. Matzger, M. O'Keeffe, O.M. Yaghi, Nature 427 (2004) 523–527.
- [20] D.J. Tranchemontagne, M.O.k.Z. Ni, O.M. Yaghi, Angew. Chem. Int. Ed. 47 (2008) 5136–5147.
- [21] S.S. Kaye, A. Dailly, O.M. Yaghi, J.R. Long, J. Am. Chem. Soc. 129 (2007) 14176– 14177.
- [22] H. Furukawa, N. Ko, Y.B. Go, N. Aratani, S.B. Choi, E. Choi, A.O. Yazaydin, R.Q. Snurr, M. O'Keeffe, J. Kim, O.M. Yaghi, Science 239 (2010) 424–428.
- [23] P. Horcajada, T. Chalati, C. Serre, B. Gillet, C. Sebrie, T. Baati, J.F. Eubank, D. Heurtaux, P. Clayette, C. Kreuz, J.S. Chang, Y.K. Hwang, V. Marsaud, P.N. Bories, L. Cynober, S. Gil, G. Férey, P. Couvreur, R. Gref, Nat. Mater. 9 (2010) 172–178.
- [24] R.J. Kuppler, D.J. Timmons, Q.-R. Fang, J.-R. Li, T.A. Makal, M.D. Young, D. Yuan, D. Zhao, W. Zhuang, H.-C. Zhou, Coord. Chem. Rev. 253 (2009) 3042–3066.
- [25] L. Ma, W. Lin, Top. Curr. Chem. 293 (2010) 175–205.
- [26] H. Li, M. Eddaoudi, M. O'Keeffe, O.M. Yaghi, Nature 402 (1999) 276–279.
- [27] J.L.C. Rowsell, O.M. Yaghi, Micropor. Mesopor. Mater. 73 (2004) 3–14.
- [28] Z.-Q. Li, L.-G. Qiu, T. Xu, Y. Wu, W. Wang, Z.-Y. Wu, X. Jiang, Mater. Lett. 63 (2009) 78–80.
- [29] B. Chen, S. Xiang, G. Qian, Acc. Chem. Res. 43 (2010) 1115–1124.
- [30] D.T. Genna, A.G. Wong-Foy, A.J. Matzger, M.S. Sanford, J. Am. Chem. Soc. 135 (2013) 10586–10589.
- [31] J.A. Mason, M. Veenstra, J.R. Long, Chem. Sci. 5 (2014) 32–51.
- [32] M.-L. Ma, C. Ji, S.-Q. Zang, Dalton Trans. 42 (2013) 10579-10586.
- [33] N.W.C. Jusoh, A.A. Jalil, S. Triwahyono, C.R. Mamat, Appl. Catal. A Gen. 492 (2015) 169–176.
- [34] M. Babazadeh, R. Hosseinzadeh-Khanmiri, J. Abolhasani, E. Ghorbani-Kalhor, A. Hassanpour, RSC Adv. 5 (2015) 19884–19892.
- [35] N.T.S. Phan, T.T. Nguyen, Q.H. Luu, L.T.L. Nguyen, J. Mol. Catal. A Chem. 363– 364 (2012) 178–185.
- [36] Z.-Y. Gu, J. Park, A. Raiff, Z. Wei, H.-C. Zhou, ChemCatChem 6 (2014) 67–75.
- [37] P. Valvekens, F. Vermoortelea, D.D. Vos, Catal. Sci. Technol. 3 (2013) 1435– 1445.

- [38] J. Liu, L. Chen, H. Cui, J. Zhang, L. Zhang, C.-Y. Su, Chem. Soc. Rev. 43 (2014) 6011–6061.
- [39] A. Corma, H. García, F.X. Llabrés i Xamena, Chem. Rev. 110 (2010) 4606-4655.
- [40] A. Dhakshinamoorthy, H. Garcia, Chem. Soc. Rev. 41 (2012) 5262–5284.
- [41] M. Yoon, R. Srirambalaji, K. Kim, Chem. Rev. 112 (2012) 1196–1231.
- [42] F. Zadehahmadi, S. Tangestaninejad, M. Moghadam, V. Mirkhani, I. Mohammadpoor-Baltork, A.R. Khosropour, R. Kardanpour, Appl. Catal. A Gen. 477 (2014) 34–41.
- [43] T. Otto, N.N. Jarenwattananon, S. Glöggler, J.W. Brown, A. Melkonian, Y.N. Ertas, L.-S. Bouchard, Appl. Catal. A Gen. 488 (2014) 248–255.
- [44] Q.-X. Luo, X.-D. Song, M. Ji, S.-E. Park, C. Hao, Y.-Q. Li, Appl. Catal. A Gen. 478 (2014) 81–90.
- [45] K. Leus, Y.-Y. Liu, M. Meledina, S. Turner, G.V. Tendeloo, P.V.D. Voort, J. Catal. 316 (2014) 201–209.
- [46] A. Dhakshinamoorthy, A.M. Asiri, H. Garcia, Chem. Soc. Rev. 44 (2015) 1922– 1947.
- [47] A.H. Chughtai, N. Ahmad, H.A. Younus, A. Laypkov, F. Verpoor, Chem. Soc. Rev., 2015, in press, doi:http://dx.doi.org/10.1039/C1034CS00395K.
- [48] P. Wu, C. He, J. Wang, X. Peng, X. Li, Y. An, C. Duan, J. Am. Chem. Soc. 134 (2012) 14991–14999.
- [49] A.S. Roy, J. Mondal, B. Banerjee, P. Mondal, A. Bhaumik, S.M. Islam, Appl. Catal. A: Gen. 469 (2014) 320–327.
- [50] N.T.S. Phan, T.T. Nguyen, P. Ho, K.D. Nguyen, ChemCatChem 5 (2013) 1822-1831.
- [51] T. Truong, V.T. Nguyen, H.T.X. Le, N.T.S. Phan, RSC Adv. 4 (2014) 52307-52315.
- [52] Y. Luan, N. Zheng, Y. Qi, J. Tang, G. Wang, Catal. Sci. Technol. 4 (2014) 925–929.
- [53] G. Yu, J. Sun, F. Muhammad, P. Wang, G. Zhu, RSC Adv. 4 (2014) 38804–38811.
- [54] Y.-R. Lee, Y.-M. Chung, W.-S. Ahn, RSC Adv. 4 (2014) 23064–23067.
- [55] A.S. Roy, J. Mondal, B. Banerjee, P. Mondal, A. Bhaumik, S.M. Islam, Appl. Catal. A. Gen. 469 (2014) 320–327.
- [56] G.H. Dang, D.T. Nguyen, D.T. Le, T. Truong, N.T.S. Phan, J. Mol. Catal. A: Gen. 395 (2014) 300–306.
- [57] G.H. Dang, T.T. Dang, D.T. Le, T. Truong, N.T.S. Phan, J. Catal. 319 (2014) 258– 264.
- [58] P. Valvekens, M. Vandichel, M. Waroquier, V.V. Speybroeck, D.D. Vos, J. Catal. 317 (2014) 1–10.
- [59] M. Savonnet, S. Aguado, U. Ravon, D. Bazer-Bachi, V. Lecocq, N. Bats, C. Pinel, D. Farrusseng, Green Chem. 11 (2009) 1729–1732.
- [60] E. Pérez-Mayoral, Z. Musilová, B. Gil, B. Marszalek, M. Položij, P. Nachtigall, J. Čejka, Dalton Trans. 41 (2012) 4036–4044.
- [61] M. Opanasenko, M. Shamzhy, J. Čejka, ChemCatChem 5 (2013) 1024-1031.
- [62] N.T.S. Phan, P.H.L. Vu, T.T. Nguyen, J. Catal. 306 (2013) 38-46.
- [63] O.V. Zalomaeva, A.M. Chibiryaev, K.A. Kovalenko, O.A. Kholdeeva, B.S. Balzhinimaev, V.P. Fedin, J. Catal. 298 (2013) 179–185.
- [64] H.T.N. Le, T.V. Tran, N.T.S. Phan, T. Truong, Catal. Sci. Technol. 5 (2015) 851– 859.
- [65] I. Luz, A. Corma, F.X.L.i. Xamena, Catal. Sci. Technol. 4 (2014) 1829–1836.
- [66] Tanmoy Maity, D. Saha, S. Koner, ChemCatChem 6 (2014) 2373–2383.
- [67] Y. Jiang, J. Huang, M. Hunger, M. Maciejewski, A. Baiker, Catal. Sci. Technol. 5 (2015) 897–902.
- [68] A. Dhakshinamoorthy, M. Alvaro, H. Garcia, Adv. Synth. Catal. 351 (2009) 2271–2276.
- [69] A. Dhakshinamoorthy, M. Alvaro, H. Garcia, Adv. Synth. Catal. 352 (2010) 711– 717.
- [70] A. Dhakshinamoorthy, M. Alvaro, H. Garcia, Adv. Synth. Catal. 352 (2010) 3022–3030.
- [71] L. Alaerts, E. Séguin, H. Poelman, F. Thibault-Starzyk, P.A. Jacobs, D.E. De Vos, Chem. Eur. J. 12 (2006) 7353–7363.
- [72] I. Luz, F.X. Llabrés i Xamena, A. Corma, J. Catal. 285 (2012) 285-291.
- [73] I. Luz, F.X. Llabrés i Xamena, A. Corma, J. Catal. 276 (2010) 134–140.
- [74] D. Ruano, M. Díaz-García, A. Alfayate, M. Sánchez-Sánchez, ChemCatChem 7 (2015) 674–681.
- [75] R. Sanz, F. Martínez, G. Orcajo, L. Wojtas, D. Briones, Dalton Trans. 42 (2013) 2392–2398.
- [76] G. Langhendries, D.E.D. Vos, G.V. Baron, P.A. Jacobs, J. Catal. 187 (1997) 453– 463.
- [77] N.T.S. Phan, C.W. Jones, J. Mol. Catal. A: Chem. 253 (2006) 123-131.
- [78] H. Wang, M. Frenklach, Combust. Flame 96 (1994) 163–170.
- [79] J. Jae, G.A. Tompsett, A.J. Foster, K.D. Hammond, S.M. Auerbach, R.F. Lobo, G.W. Huber, J. Catal. 279 (2011) 257–268.
- [80] Y. Kubota, M. Takata, R. Matsuda, R. Kitaura, S. Kitagawa, T.C. Kobayashi, Angew. Chem. Int. Ed. 45 (2006) 4932–4936.
- [81] R. Bai, G. Zhang, H. Yi, Z. Huang, X. Qi, C. Liu, J.T. Miller, A.J. Kropf, E.E. Bunel, Y. Lan, A. Lei, J. Am. Chem. Soc. 136 (2014) 16760–16763.
- [82] M. Maes, S. Schouteden, K. Hirai, S. Furukawa, S. Kitagawa, D.E. De Vos, Langmuir 27 (2011) 9083–9087.
- [83] S.S.-Y. Chui, S.M.-F. Lo, J.P.J. Charmant, A.G. Orpen, L.D. William, Science (1999) 1148–1150.
- [84] J. Liu, B. Lukose, O. Shekhah, H.K. Arslan, P. Weidler, H. Gliemann, S. Bräse, S. Grosjean, A. Godt, X. Feng, K. Müllen, I.-B. Magdau, T. Heine, C. Wöll, Sci. Reports 2 (2012) 921.
- [85] C.G. Carson, K. Hardcastle, J. Schwartz, X. Liu, C. Hoffmann, R.A. Gerhardt, R. Tannenbaum, Eur. J. Inorg. Chem. (2009) 2338–2343.
- [86] A.N. Mlinar, B.K. Keitz, E.D. Gygi, D. Bloch, J.R. Long, A.T. Bell, ACS Catal. 4 (2014).

- [87] C. Volkringer, M. Meddouri, T. Loiseau, N. Guillou, J. Marrot, G. Férey, M. Haouas, F. Taulelle, N. Audebrand, M. Latroche, Inorg. Chem. 47 (2008) 11892– 11901.
- [88] J.H. Cavka, S. Jakobsen, U. Olsbye, N. Guillou, C. Lamberti, S. Bordiga, K.P. Lillerud, J. Am. Chem. Soc. 130 (2008) 13850–13851.
- [89] T.G. Glover, G.W. Peterson, B.J. Schindler, D. Britt, O.M. Yaghi, Chem. Eng. Scien. 66 (2011) 163–170.
- [90] L.T.L. Nguyen, T.T. Nguyen, K.D. Nguyen, N.T.S. Phan, App. Catal. A Gen. 425– 426 (2012) 44–52.
- [91] H. Furukawa, J. Kim, N.W. Ockwig, M. O'Keeffe, O.M. Yaghi, J. Am. Chem. Soc. 130 (2008) 11650–11661.
- [92] K. Tan, N. Nijem, P. Canepa, Q. Gong, J. Li, T. Thonhauser, Y.J. Chabal, Chem. Mater. 24 (2012) 3153–3167.
- [93] N.T.S. Phan, C.K. Nguyen, T.T. Nguyen, T. Truong, Catal. Sci. Technol. 4 (2014) 369–377.
- [94] D. Britt, H. Furukawa, B. Wang, T.G. Glover, O.M. Yaghi, PNAS 106 (2009) 20637–20640.
- [95] D. Feng, W.-C. Chung, Z. Wei, Z.-Y. Gu, H.-L. Jiang, Y.-P. Chen, D.J. Darensbourg, H.-C. Zhou, J. Am. Chem. Soc. 135 (2013) 17105–17110.
- [96] D. Liu, T.-F. Liu, Y.-P. Chen, L. Zou, D. Feng, K. Wang, Q. Zhang, S. Yuan, C. Zhong, H.-C. Zhou, J. Am. Chem. Soc. 137 (2015) 7740–7746.
- [97] Z. Zhang, H. Yoshikawa, K. Awaga, J. Am. Chem. Soc. 136 (2014) 16112–16115.
- [98] T. Arai, N. Kawasaki, H. Kanoh, Synlett 23 (2012) 1549–1553.
- [99] G.-G. Pila, M. Müller, A. Corma, Chem. Sci. 5 (2014) 2979–3007.