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Cu (I)-functionalized SBA-16: an efficient catalyst for the synthesis of α -ketoamides under moderate conditions

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An efficient catalyst based on cage-like mesoporous material SBA-16 as support and Cu(I) as active sites has been successfully prepared. The catalyst demonstrated the high catalytic activity (up to 88%) in the direct oxidative synthesis of α -ketoamides between acetophenone and piperidine, employing O₂ from open air as oxidant without other additives. Meanwhile, the heterogeneous catalyst was first time to be applied for this reaction, and the catalyst could be easily separated from the reaction system by filtration and reused for several times without a significant loss of activity.

1 Introduction

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The α -ketoamides are the key structural element of a large amount of natural products, pharmaceuticals and synthetic agents, which have been paid considerable attention due to their significant biological activities.¹⁻⁹ Meanwhile, the α ketoamides are irreplaceable intermediates for the further transformation to $\alpha\text{-diones}$ and $\beta\text{-lactams},$ etc. $^{10\text{-}12}$ There are several traditional methods for the synthesis of α -ketoamides: double carbonylation of aryl iodides, $^{\rm 13\text{-}15}$ the reaction of pyruvic or benzoylformic acid with allyl amine,¹⁶ amidation of $\alpha\text{-keto}$ acids and $\alpha\text{-keto}$ acyl halides, 17 the reaction between acyl chlorides and r-isocyanoacetamides via the following acid hydrolysis,¹⁸ the coupling of formamides and α -oxocarboxylic acids.^{19, 20} However, these methods suffer from the drawbacks of hazardous reagents, harsh conditions and the limitation of precursor availability. Therefore, the development of mild, convenient and efficient methods toward α -ketoamides is still required.

In 2009, Ning Jiao and his coworkers²¹ reported the oxidative amidation diketonization of terminal alkynes catalyzed by CuBr to synthesize α -ketoamides, in which molecular oxygen was used as the oxidant at low temperature. Since then, aerobic oxidative reactions have been developed into efficient and environmental friendly strategies for the synthesis of α ketoamides. Jiao *et al^{22}* developed the coupling of aryl acetaldehydes with anilines leading to α -ketoamides, and in this process cheaper materials were employed. Meanwhile, the ¹⁸O labelled products were studied, the result turned out that the oxygen atoms of carboxides were all from molecular oxygen. And then, Jianxin Ji and his company²³ reported the synthesis of α -ketoamides by aryl methyl ketones, amines and molecular oxygen, and the reaction had a good yield at lower temperature without other additives. Subsequently, metalfree methods were further explored to reduce the costs, especially in the last two years. TBHP/I₂ promoted oxidative coupling of acetophenones with amines,²⁴ and the synthesis of α -ketoamides via I₂-catalysed oxidative coupling of acetophenones with formamides,²⁵ etc. However, the difficulties of the separation of the catalyst from the reaction system restrict the application of these homogeneous catalysts.

Compared with homogeneous catalysts, heterogeneous catalysts have the advantages of keeping stable activity and selectivity, being separated from the reaction systems easily, excellent reusability ,and saving resources and energy. In other words, heterogeneous catalysts are more effective, convenient and environmental friendly than the homogeneous ones. In consideration of these superiorities, novel heterogeneous catalysts should be developed to be applied in synthesizing α ketoamides. It's another way to reduce the cost. In recent years, a large number of methods have been developed to immobilize metal active sites on numerous solid supports, such as polymeric microspheres, microcapsules and resin,²⁶⁻²⁸ mesoporous materials,^{29, 30} amorphous silica³¹ and carbon nano fibers.³² Among various supports of the heterogeneous catalysts, the mesoporous materials have the great superiority due to their regularly arranged pore structure,³³ large specific surface area and great hydrothermal stability. In the numerous catalysts, the combination of copper and solid support is in great need. Of course, the copper-based catalysts can be employed in the reaction leading to α -ketoamides, which have been successfully applied to other reactions. $^{\rm 34,\,35}$

SBA-16, a cage-like mesoporous framework, has good pore connectivity and unique structure for the passage of large molecules such as organic reactants and metal complexes,³⁶ and it is superior to other widely-used channel-like materials (e.g. MCM-41 and SBA-15). This material owns tunable cage size (4-10 nm) and pore entrance size, together with large surface area >700 m² g⁻¹. It is generally believed that high surface area could combine with more active sites and provide a highly dispersed system.³⁷

To the best of our knowledge, so far few studies have reported the immobilized SBA-16-Cu catalyzing the synthesis of α ketoamides. In this work, we developed a new copper (I) bounded catalyst through functionalized 3D-hexagonally ordered SBA-16 type material with triethoxysilylpropyl isocyanate followed by the grafting with L-4-hydroxyproline. Furthermore, the catalytic activity and reusability of the catalyst were systematically evaluated in the synthesis of the α -ketoamides.

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2 Experimental

2.1. Materials

Pluronic P123 (EO₂₀PO₇₀EO₂₀) and F127 (EO₁₀₆PO₇₀EO₁₀₆) were purchased from Sigma–Aldrich. Triethoxysilylpropyl isocyanate was supplied by Alfa Aesar. Cul (98%) was obtained from Tianjin Guangfu Fine Chemical Research Institute. Acetophenone and its derivatives together with piperidine were purchased from Sinopharm Chemical Reagent Co., Ltd. Tetraethoxysilane and other reagents were obtained from Tianjin Guangfu Fine Chemical Research Institute. THF, toluene were redistilled, other solvents were analytical grade and used without further purification. Deionized water was used throughout the experiments.

2.2. Syntheses of mesoporous silica materials

Mesoporous materials SBA-16, SBA-15 and MCM-41 were prepared as the method given in previous reports. $^{\rm 38-40}$

2.2.1 Synthesis of SBA-16 Pluronic F127 (1.484 g) was used as the templates and P123 (0.238 g) acted as the surface-active agent. The mixture of the two was completely dissolved in a solution of 60 mL of deionized water and 8.87 mL of concentrated hydrochloric acid (36%), the solution was magnetically stirred at 40 °C for 4 h. Then, 5.6 mL of tetraethylorthosilicate was added dropwise to the solution in 12-15 min. After being magnetically stirred for 45 min, the resulting suspension was transferred into a Teflon autoclave. The autoclave was placed under stable conditions at 40° C for 24 h. Subsequently, the temperature of the autoclave was raised up to 100° C, and kept at this temperature for 32 h. After the hydrothermal treatment, the precipitated solid was isolated by filtration, dried in air at room temperature, yielding white powders. The products were calcined at 550 $^\circ\!\mathrm{C}$ for 10 h to remove the templates. Thus, the final mesoporous silica material was obtained.

2.2.2 Synthesis of SBA-15 2 g of P123 as the surface-active agent was dissolved in 30 g of deionized water and 120 g of 2 M HCl with stirring at 38 $^{\circ}$ C, which followed by adding 8.5 g of TEOS and stirring for 20 h. The milky mixture was transferred into an autoclave and aged at 100 $^{\circ}$ C for 48 h. The solid was harvested by filtration, washed with deionized water, dried at room temperature, and calcined in air at 550 $^{\circ}$ C for 6 h to obtain the SBA-15

2.2.3 Synthesis of MCM-41 The structure-directing agent is cetyltrimethylammonium bromide (CTAB), the MCM-41 was prepared by adding 5.78 g of TEOS to an aqueous solution containing 1.01 g of CTAB and 0.34 g of NaOH and 30 mL of deionized water. After stirring at room temperature for 1 h, the resulting mixture was transferred to a Teflon autoclave to crystallization under static hydrothermal conditions at 100°C for 48 h. The obtained solid product was filtered, washed with deionized water to remove sodium ions until the pH of the solution was 7. The filtered precipitate was dried at room temperature and calcined in air at 550°C for 5 h to remove the CTAB.

2.3. Preparation of the SBA-16-pro- Cu (I)

2.3.1 Synthesis of compound 2 Under ice bath, L-4-



hydroxyproline (40 mmol, 5.245 g) and NaHCO₃ (120 mmol,

Scheme 1 The preparation of the SBA-16-pro-Cu (I)

10.08 g) were added in acetone (40 mL) and distilled water (80mL). With continuously stirring, benzyl chloroformate (48 mmol, 8.18 g) dissolved in acetone (12 mL) was added dropwise to the mixture. After the dropwise, the mixture was kept stirring in ice environment for 30 min and followed by reacting at room temperature for 2 h. Then the pH of the reaction system was adjusted to 3-4 with 1 mol/L HCl, and acetone was removed by vacuum distillation. The resulting solution was extracted by $CH_3COOC_2H_5$ (4×60 mL). The organic layer was combined and dried by anhydrous Na_2SO_4 , and then it was filtered and evaporated. Compound 2 ((2S)-1-((benzyloxy) carbonyl) -4-hydroxypyrrolidine-2-carboxylic acid) was obtained.

2.3.2 Synthesis of compound **3** Triethylamine (49.5 mmol, 4.99g, 7.15 mL) was added to the solution of compound 2 (12.23 g, 45 mmol) and benzyl bromide (49.5 mmol, 8.47 g, 5.90 mL) in THF (50 mL) at 0°C. The solution was stirred for 18h at room temperature, after that, the mixture was evaporated in vacuo to remove the solvent. Dissolve the rest in 50 mL of CH₂Cl₂, and wash with HCl (1N), H₂O, Na₂CO₃ (5%), and H₂O successively. Then the oil phase was dried over Na₂SO₄, and evaporated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate=2:1) to obtain the compound 3 ((2S)-dibenzyl 4-hydroxypyrrolidine-1, 2-dicarboxylate), which appears as pale yellow oil.

2.3.3 Synthesis of compound 4 The compound 3 (10 mmol, 3.55 g), triethoxysilylpropyl isocyanate (15 mmol, 3.71 g, 3.71 mL) and triethylamine (20 mmol, 2.02 g, 2.89 mL) were mixed in THF (25 mL), followed by refluxing for 24 h. After cooling to room temperature, vacuum distillation was used to remove solution. The product was purified by column chromatography on silica gel (hexane/ethyl acetate=4:1) to afford compound 4 ((2S)-dibenzyl 4-(((3-(triethoxysilyl) propyl) carbamoyl) oxy) pyrrolidine-1, 2-dicarboxylat e) as a brown oil.

2.3.4 Synthesis of compound 5 Compound 5 was given by the hydrogenation of compound 4. Compound 4 (6.7 mmol, 4.08 g) and the catalyst Pd/C (273 mg, 7%) were added to autoclave in methanol (40 mL). The reaction was conducted at 35° C,

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under H_2 atmosphere (5 atm) for 7 h. After the reaction, the catalyst was filtered off, and the filtrate was evaporated. The resulting pale yellow oil is compound 5, without further purification.

2.3.5 Synthesis of SBA-16-pro Compound 5 (725 mg) was dissolved in toluene (10 mL) and added into the suspension of the support SBA-16 (870 mg) which dissolved in toluene (40 mL). The mixture was refluxed for 24 h. After the reaction system was cooled down, the mixture was filtered. The resulting solid was washed with a series of solvents with different polarity (methanol, ethyl acetate, CH_2Cl_2 and ether) abundantly. It's aiming at removing the residual non-supported proline derivative. The solid was SBA-16-pro and was dried at 40°C under vacuum. At the same time, SBA-15-pro and MCM-41-pro were synthesized using the same method.

2.3.6 Synthesis of the catalyst SBA-16-pro-Cu (I) A mixture of modified mesoporous silica (500 mg) and cuprous iodide (95 mg) in THF (30 mL) was refluxed for 4 h under continuously stirring to obtain the catalyst. Then the catalyst was filtered, washed with several solvents (ethanol, ethyl acetate, CH_2Cl_2) abundantly and dried at 40°C under vacuum. The resulting solid was SBA-16-pro-Cu (I). Meanwhile, SBA-15-pro-Cu (I) and MCM-41-pro-Cu (I) were synthesized in the same way.

All the procedures except the hydrogenation were carried out under an atmosphere of nitrogen. Scheme 1 shows the synthesis process and the structure of the functional molecule. 2.4 Characterization of the catalyst SBA-16-pro-Cu (I)

2.4 Characterization of the catalyst SBA-10-pro-Cu (I)

The synthesized catalyst was confirmed by corresponding characterization means.

Powder X-ray diffraction (XRD) patterns were carried out at room temperature and performed on a Rigaku D/max-2400 diffractometer using Cu-Ka radiation as the X-ray source in the 20 range of 0.5-4 and 10-90 for small angle and wide angle, respectively. Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet NEXUS 670 FTIR spectrometer with a DTGS detector, and samples were measured with KBr pellets. The morphology and microstructure of SBA-16-pro-Cu (I) were characterized by transmission electron microscopy (TEM). The TEM images were obtained through Tecnai G2 F30 electron microscope operating at 300 kV, and the samples were obtained by placing a drop of a colloidal solution onto a copper grid and evaporating the solvent in air at room temperature. N₂ physical sorption was carried out on micromeritics ASAP2020 volumetric adsorption analyzer (before the measurements, samples were out gassed at 120° C for 6 h). The Brunauer-Emmett-Teller (BET) surface area was evaluated from data in the relative pressure range from 0.05 to 0.20. The total pore volume of each sample was estimated from the amount adsorbed at the highest P/P_0 (above 0.99). Pore diameters were determined from the adsorption branch using Barrett-Joyner-Halenda (BJH) method. The conversion was estimated by GC-MS (Agilent 6,890N/5,973N).

2.5 The reaction procedure in the synthesis of α -ketoamide.

2.5.1. Optimization experiments of reaction. Acetophenone (0.25 mmol, 30 mg), piperidine (0.5 mmol, 42.6 mg) and corresponding amounts of catalysts were added to the reaction system. The reaction mixture was stirred for 8-30 h



Fig.1. Small angle XRD patterns of (a) SBA-16 , (b) SBA-16-pro-Cu (I) and (C) used SBA-16-pro-Cu (I)



Fig. 2 FT-IR spectra of (a) SBA-16, SBA-16-pro and SBA-16-pro-Cu(l) and (b) the enlargement of the region at around 1450-1750 $\rm cm^{-1}$

under the presence of oxygen. The solvent and temperature of reactions were selected. After the reaction, the catalyst was filtered, and the filtrate was analyzed by GC-MS.

2.5.2 The reaction between different acetophenone derivatives and amines. The corresponding acetophenone derivatives (0.25 mmol), amines (0.5mmol) and the catalyst SBA-16-pro-Cu (I) (15 mol %) were stirred in 2 mL EtOAc for 16 h at 50 $^{\circ}$ C. After the separation of the catalyst, the mixture was determined by GC-MS.

2.5.3 Recycling tests of catalyst SBA-16-pro-Cu (I) Acetophenone (0.25 mmol, 30 mg), piperidine (0.5 mmol, 42.6 mg) and the catalyst SBA-16-pro-Cu (I) (15 mol %) were mixed in 2 mL EtOAc and stirred for 16 h at 50° C. The catalyst was filtered and washed with EtOAc for several times, then dried under vacuum. In next run, another portion of reactants was added. The products in every recycling were isolated by filtration and analyzed by GC-MS.

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3 Results and discussions

3.1 Characterizations of the catalyst SBA-16-pro-Cu (I)



Fig. 1 showed the small-angle X-ray diffraction patterns of SBA-16, SBA-16-pro-Cu (I) and the used SBA-16-pro-Cu (I). The pattern of fresh SBA-16 showed a strong diffraction peak and two small diffraction peaks for the (110), (200) and (211) planes. All the peaks indicated that SBA-16 had a well-defined hexagonal symmetry and had long-range ordering of structure. After the formation of Cu complex in SBA-16, the ordered cubic mesoporous structure of the material remained intact while the intensity of the peaks had an overall reduction. The results demonstrated that the presence of guest moieties on the mesoporous framework of SBA-16 resulted in the decrease of crystallinity, but not collapsed of the pore structure of mesoporous materials. Compared with the pattern of fresh SBA-16, after the reaction the structure of SBA-16 was well maintained.

The FT-IR spectra of SBA-16, SBA-16-pro and SBA-16-pro-Cu (I) were displayed in Fig. 2. The spectrum of SBA-16 exhibited a broad band at 1646 cm-1 due to O-H bending vibration of the water absorbed on the solid surface. The bands at 960 cm-1 and 1085 cm-1 were assigned to the typical Si-OH stretching vibration and Si-O-Si vibrations, respectively. The band at 960 cm-1 had a significant decrease after grafting with L-4hydroxyproline, which showed that L-4-hydroxyproline have been attached to the SBA-16 matrix. Compared with the spectrum of SBA-16, there were three new peaks near 2983, 1709 and 1529 cm-1 obviously appearing in that of SBA-16-pro and SBA-16-pro-Cu (I), which were related to the stretching vibrations of C-H, carboxylic C=O, and the bending vibration of N-H in proline, respectively ^{41, 42}. These results indicated that SBA-16 was successfully functionalized by L-4-hydroxyproline and the structure of the silicon material SBA-16 was retained. In Fig. 2 (a), the C=O and N-H stretching frequencies of SBA-16-pro shifted from 1709, 1529 cm-1 to 1700 and 1528 cm-1 (higher frequencies in the spectrum of SBA-16-pro-Cu (I)), and the shift indicated the formation of the Cu complex.

The TEM images of SBA-16 and SBA-16-pro-Cu (I) were shown in Fig. 3. The SBA-16 matrix revealed highly ordered arrangements of uniform channels, which illustrated that the material was consist of a high-quality body-centered cubic mesostructure (Fig. 3a). After decorated by L-4-hydroxyproline and coordinating with Cul, the ordered arrangements were still well maintained (Fig. 3b).

Table 1 Structural parameters of SBA-16 and SBA-16-pro-Cu(I)						
Samples	BET surface area(m ² g ⁻¹)	Pore volume (cm ² g ⁻¹)	Pore size (nm)			
SBA-16	778.64	0.955	6.32			
SBA-16-pro-	225.39	0.356	4.90			







Fig. 5 XPS spectra of the (a) SBA-16-pro-Cu (I) and (b) SBA-16-pro-Cu (I) after a run

The nitrogen physisorption isotherms and pore size distributions of SBA-16-pro-Cu (I) and SBA-16 were plotted in Fig. 4. Both of the curves exhibited type IV isotherm patterns with type H2 hysteresis loops at relative pressure in the range of 0.4 and 0.8 for a typical mesoporous material with inkbottle pores and pore network connectivity like SBA-16. The sorption isotherms adjusted to the H2 hysteresis loops, indicating the materials had relatively uniform channel-like pores and the cage-like structure was maintained after the SBA-16 grafted with proline. Meanwhile, considerable decreases of the surface area, pore size and pore volume were observed. The parameters which were calculated from the adsorption branch by using the BJH model were listed in Table 1. These changes proved the proline was immobilized not only on the external surface of SBA-16 but also into the interior.

The catalyst SBA-16-pro-Cu (I), SBA-16-pro-Cu (I) after a run and the elemental state of the materials were analyzed by X-ray photoelectron spectroscopy (XPS) (shown in Fig. 5). The peaks at 101.6, 282.5, 399.9 and 530.4 eV were attributed to Si, C, N and O atoms, respectively. Meanwhile, the peak of iodine appeared clearly at 621.6 eV and 633.5 eV. At the Cu 2p level, the $2p_{1/2}$ and $2p_{3/2}$ were shown at 951.6 and 931.7 eV, respectively. The peak positions observed here were in

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agreement with the expected for Cu (I) species, 43 which confirmed the nonexistence of Cu (II) species. The XPS result



Fig. 6 wide angle XRD patterns of SBA-16-pro- Cu (I)

showed that Cu (I) was not oxidized to Cu (II) (The conclusion was also revealed in XRD studies). After a run, the intensity of the peaks of Cu 2p $_{3/2}$, Cu 2p $_{1/2}$ and I 3d $_{5/2}$, I 3d $_{3/2}$ have declined. The decline indicated the decrease of the loading of Cu, corresponding to the drop of the ICP analysis of Cu (I) after first run.

The wide-angle XRD of the SBA-16-pro-Cu (I) was obtained (Fig. 6). Compared with the standard, the XRD pattern of the catalyst agreed well with CuI standard (Fac. Chem. Formula 00-006-0246), which proved that the Cu (I) has not been oxidized to Cu (II). The valence of Cu was remained after being immobilized on functionalized SBA-16.

Through elemental analysis of C, H and N, the N content of SBA-16-pro-Cu (I) was evaluated to be 2.48% (wt %), the ICP analysis showed that the Cu content was 4.07% (wt %) in SBA-16- pro-Cu (I).

3.2 Catalytic activity

The catalytic activity of SBA-16-pro-Cu (I) was tested by employing aryl methyl ketones and amines. The reaction between acetophenone (1a) and piperidine (2a) was used as model substrates to optimize the reaction conditions (Table 2 and Fig. 7) under open air. Influencing factors for the reaction, including the amount of the catalyst, temperature, solvent and reaction time, were investigated one after another and then the reaction results were tested by GC-MS. In most reaction systems, the amide by-product was detected and thus the selection of parameters based on the selectivity and yield of the reactions. At first, we investigated the influence of amount of the catalyst to reaction system. With the amount of catalyst increasing to 15 mol %, both selectivity and yield had apparently improvement. When the amount rose up to 20 mol %, the yield decreased (entries 1-4). According to above discusses, 15 mol % was the best catalyst amount. With reaction temperature reducing, the selectivity gradually rose along with the appreciably decrease of the yield (entries 4-7). The reaction in THF at 50 $^{\circ}$ C gave 1-phenyl-2-(piperidin-1-yl) ethane-1, 2-dione (3aa) in 51% yield (entry 3). With other solvents like MeOH, toluene, DMF and so on, the yields were different (entries 8-15). The screening of a range of solvents showed that the ethyl acetate (EtOAc) was the most effective solvent, affording 3aa in 69% yield (entry 15). The results of the reactions proceeding for different times were lined in Fig. 7. From 8 to 16 h, the yields had notable growth. After being conducted 16h, the yields of the reaction reached equilibrium; while the selectivity declined with the time extension. It is obvious that the optimum time is 16h. After an extensive screening of the reaction parameters, the best yield of 3aa (88%) was obtained when the catalyst amount was 15mol% in EtOAc for 16 h under an air atmosphere (entry 16). No desired products were observed in the absence of catalyst (entry 17) and the addition of equal mass of 15 mol % SBA-16 (entry 18) and SBA-16-pro (entry 19).

As the base is necessary for the coupling reaction, the amount of piperidine was also investigated. When the amount of piperidine was 1 equiv, the reaction gave 3aa in 29% yield (Table 3, entry 1). With increasing the amount of piperidine from 1 equiv to 3 equiv, both the selectivity and the yield had increases, and the 3 equiv was slightly superior to 2 equiv. With the amount of piperidine rising from 3 equiv to 5 equiv, the selectivity increased while the yield declined. From an economical point of view, 2 equiv of piperidine was the preferred amount.



Fig. 7 The variation of a-ketoamide with reation time in the reaction of acetophenone (1a) with piperidine (2a). Yields were determined by GC-MS.

Table 2 Optimization conditions of the reaction leading to α -ketoamides



Entry	Loading (mol %)	Solvent	Temperature (°C)	Time (h)	Conversion (%)	Selectivity (%)	Yield ^a (%)
1	5	THF	50	12	38	67	26
2	10	THF	50	12	40	66	26
3	15	THF	50	12	68	76	51
4	20	THF	50	12	48	78	37
5	15	THF	RT	12	26	92	23
6	15	THF	30	12	44	84	37
7	15	THF	40	12	49	77	38
8	15	MeOH	50	12	28	68	20
9	15	toluene	50	12	49	86	42
10	15	DMF	50	12	42	84	36
11	15	CH3CN	50	12	31	89	28
12	15	EtOH	50	12	14	85	12
13	15	1,4-dioxane	50	12	62	87	54
14	15	DMSO	50	12	46	87	40
15	15	EtOAc	50	12	72	90	65
16	15	EtOAc	50	16	96	92	88(81) ^d
17	—	EtOAc	50	16	—	—	_
18	SBA-16 ^b	EtOAc	50	16	—	—	
19	SBA-16-pro ^c	EtOAc	50	16	—	—	_
20	SBA-15-pro-Cu (I)	EtOAc	50	16	90	81	73
21	MCM-41-pro-Cu (I)	EtOAc	50	16	84	80	67

^a The conversion and yield was determined by GC–MS ^b The mass equal to 15 mol% SBA-16 was added ^c The mass equal to 15 mol% SBA-16-pro was added ^d The isolated yield

In view of the porosity of SBA-16, the reaction could be conducted both on the surface and in the channel. According to Scheme 2, the channel improved the reactivity and gained a higher yield.³⁷ With the optimized parameters, CuI was employed to the reaction, which afforded the desired product in 77% yield (Scheme 2, a); While both CuI and L-proline were used for the synthesis, the reaction exhibited a lower yield due

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^aReaction conditions: 1 (0.25mmol), 2a (2.0 equiv.), SBA-16-pro-Cu (I) (15%), in THF(2 mL), 50°C, 12 h, under air ^b The conversion and yield was determined by GC–MS



Scheme 2 Effects of different catalysts

to the competition between L-proline and piperidine (Scheme 2, b), and when SBA-16-pro-Cu (I) was used for the synthesis, the reaction exhibited a higher yield (Scheme 2, c). As SBA-15-pro-Cu (I) and MCM-41-pro-Cu (I) were employed as catalysts, the reaction gave yields of 73% and 67%, respectively, which indicated that SBA-16 was the better porous material and had the better pore structure. (Table 2, entry 20 and entry 21). Briefly, SBA-16 is the suitable support for the reaction.

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Table 4 Scope of aryl methyl ketones ^a	- Entry	Ar	product	conversio n (%)	Selectivit y (%)	Yiel d (%) ^b
$Ar \xrightarrow{O} + (N) \xrightarrow{Ar} + (N) \xrightarrow{Ar} + (N) \xrightarrow{Ar} + (N) \xrightarrow{Ar} + (N) \xrightarrow{O} + (N) $	1	Ib Official	Jba	95	86	82
	2	O Ic	Jon Sca	83	90	75
	3	Br O Id	Br O Jda	86	100	86
	4		CI N 3ca	89	93	83
	5	ci lf	ci Jan	85	86	73
	6	H ₃ CO lg	H ₃ CO 3ga	90	91	82
	7	F lh	F Jha	94	94	88
	8	F O Li	F O N Jia	95	95	91
	9	O ₂ N lj	O ₂ N Jja	81	95	77
	10	O ₂ N	O ₂ N	91	95	86
	11	HO O II	HO N 3la	66	92	61
	12	HO Im	HO Jma	72	100	72
	13	OH O	OH O Jana	98	71	70
	14	o lo	Joan N N	92	93	86

15	N lp	N Jpa	35	94	33
16	HO lq	HO Jqa	88	73	64
17	CI CI Ir	CI Jra	90	96	86
18	H ₂ N Is	H ₂ N N N N N N N N N N	56	63	35
19		O N 3ta	95	89	85

^aReaction conditions: 1 (0.25mmol), 2a (2.0 equiv.), SBA-16-pro-Cu (I) (15%), in EtOAc (2 mL), 50°C, 7-30 h, under air ^b The conversion and yield was determined by GC-MS

With the optimized conditions, the catalyst SBA-16-pro-Cu (I) was tested to the scope of the aryl methyl ketones, in which various groups containing both electron-donating and electron-withdrawing were employed. The results were summarized in Table 4. Generally, reactions between piperidine and aryl methyl ketones proceeded efficiently, giving the desired products with moderate to good yields under mild conditions. A wide range of functionalities such as halogen, nitro, methyl, hydroxyl groups were applied under reaction conditions. The results indicated that ketones bearing electron-withdrawing groups were good substituents and gave good yields within 20 h. The ketones attaching halogen groups gave good yields entirely, in 73-88% yield (entries 3-5, 7-8, 17); especially the generation of 3ha cost only 7 h in 88% (entry 7). Nevertheless, ketones bearing electron-donating substituents not only proceeded less efficient but also needed more time to give good yields. 1-(m-tolyl) ethanone, 1-(p-tolyl) ethanone and 1-(2, 4-dimethylphenyl) ethanone with weak donors achieved yields in 82%, 75%, 86%, respectively (entries 1, 2, 14). Notablely, the naphthyl-substituted ketone was also tolerated in this transformation, generating 3ta in 85% yield (entry 19). Meanwhile, the hydroxyl groups needed more reaction time (30 h) to attain corresponding yields (entries 11-13). Functional groups on the different positions of ketones had slight effect on the efficiency and groups on the metaposition were superior to para-position. (entries 1 and 2, 4 and 5, 9 and 10).

Table 5 Scope of amines ^a



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Entry	Amine	product	conversio n (%)	Selectivit y (%)	Yield ^b (%)
1	N H 2b		85	94	80
2		O N N Jac	92	78	72
3	H H 2d	O N J ad	18	100	18
4	N H 2e	Q Jac	83	90	75
5	$\bigcup_{\substack{N\\H}} \ 2f$		57	100	57
6	$\left(\begin{array}{c} 0 \\ N \\ H \end{array} \right) 2g$	O N O A A A A A A A A A A A A A A A A A	92	87	80
7	$\begin{bmatrix} I\\N\\H \end{bmatrix}$ 2h	O N Jaho	78	100	78
8	HN 2i	O N N N N N N N N N N N N N N N N N N N	89	79	70
9	H ₂ N 2j	O H O J Jaj	53	64	34
10	NH ₂ 2k		79	52	41
11	NH 21 °		24	100	24
12	HN 2m		13	100	13
13	NH ₂ 2n		_	_	_

^a Reaction conditions: 1a (0.25mmol), 2 (2.0 equiv.), SBA-16-pro-Cu (I) (15%), in EtOAc (2 ml), 50 °C, 12-30 h, under air b The conversion and yield was determined by GC-MS

With respect to amines, the copper-catalyzed aerobic oxidative coupling leading to α -ketoamides were investigated in Table 5. The results indicated that secondary aliphatic

amines (cyclic and acyclic) (entries 1–8) could be smoothly transformed into the desired products in moderate to high yields. Surprisingly, diisopropyl amine (2d) obtained the desired product (3ad) in a fairly low yield in 18 %, even if the reaction time was extended to 30 h (entry 3). It is supposed that the effect of steric hindrance led to the low yield. In addition, primary amines and amides generated the corresponding products in low yields (entry 9-12). The amide by-products were largely formed in the reaction of benzylamine and cyclohexanamine (entries 9-10), which revealed an unsatisfactory result. When anilines were employed in the present reaction, desired products were not obtained (entry 13).

In the following investigation, some substrates with good yields were chosen to further testify the catalytic activity. It

Table 6 Scope of ketones and amines ^a

Entr



у	лі	e	product	(%)	y (%)	(%) ^b
1	1b	2b		93	94	87
2	1c	2b	Scb N	88	94	83
3	le	2b	CI C	73	100	73
4	lj	2b	O ₂ N J _{3jb}	93	90	84
5	1c	2g	Scg ^O N	84	86	72
6	1b	2g	Sbg ^O	80	86	69
7	1b	2i		79	81	64
8	1c	2i		91	71	65

^a Reaction conditions: 1 (0.25mmol), 2a (2.0 equiv.), SBA-16-pro-Cu (I) (15%), in EtOAc(2 mL), 50°C, 16–20 h, under air ^b The conversion and yield was determined by GC–MS



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Fig. 8 Recycling experiments of the catalyst SBA-16-pro-Cu (I) for the reaction between acetophenone and piperidine

was obvious that good yields with excellent selectivity were obtained (Table 6).

3.3 The reusability of the catalyst

_Finally, we examined the recovery and reuse of the catalyst. After completion of reaction, SBA-16-pro-Cu (I) could be easily _separated from the reaction system though being filtrated and washed by stirring in EtOAc. So it could be used in the successive cycles. As Fig. 8 shown, the reusability of the catalyst in the reaction of acetophenone and piperidine was detected under identical conditions. Through the ICP analysis, after the first run the amount of Cu (I) immobilized on the silica have decrease from 4.07% to 3.29% while in the later runs the wastage has not been obtained. As a result, the yield has a slight reduction after second run while in the following runs the yields were almost equilibrated (Fig. 8, Run 3-5).

3.4 Plausible mechanism for the synthesis of α -ketoamides

Based on the recent reports^{23, 44}, a possible mechanism for the synthesis of α -ketoamides was shown in Scheme 3. The reaction was conducted by the transformation of Cu (I) and Cu (II) and the transformation was driven by O₂ and O⁻. The process, oxidation of α -position of carbonyl by NHR₁R₂, was conducted twice to achieve the radicals (in the beginning and 5 to 6), and then the generated radicals were captured by O₂. After that, the intermediate **7** which was attacked by NHR₁R₂ facilitated the formation of vital intermediate **8**. At last, the O-O cleavage led to α -ketoamides and C-O cleavage gave amide by-product.

8.

9.

24.



Scheme 3 A plausible mechanism for the supported Cu (I) - mediated synthesis of $\alpha\xspace$ ketoamides

4 Conclusions

product

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In conclusion, a simple and efficient heterogeneous catalyst SBA-16-pro-Cu (I), which immobilizes CuI on the mesoporous material SBA-16-, has been successfully prepared and used in the direct oxidative synthesis of α -ketoamides via a one-pot process without other additives. The notable features of the reactions are moderate to good yields, readily available starting materials, mild conditions and utilization of air as the oxygen source (instead of an O₂ balloon). Especially, the reusability of reaction, achieving the aims of easily recovering, keeping stable catalytic activity, environment protection and energy conservation, provides a novel approach to α -ketoamides.

Physical data of compounds isolated

1-phenyl-2-(piperidin-1-yl)ethane-1,2-dione (3aa) yellowish oil ¹H NMR (CDCl₃, 400 MHz, ppm): δ = 7.97-7.95 (d, *J* = 7.4 Hz, 2H), 7.67-7.63 (t, *J* = 7.4 Hz, 1H), 7.54-7.51 (t, *J* = 7.7 Hz, 2H), 3.72 (m, 2H), 3.32-3.29 (t, *J* = 5.6 Hz, 2H), 1.72-1.70 (m, 4H), 1.56 (m, 2H);

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