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An Efficient Nanoparticle-Supported and Magnetically Recoverable Copper(I) Catalyst for Synthesis of Furans from Ene-yne-ketone

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A magnetic nano-supported Cu(I) catalyst was prepared and showed high activity for cyclization of ene-yne-ketone to synthesize furans. The catalyst was easily recovered from the reaction by using external magnets and reused 8 times without significant loss of its catalytic activity.

Keywords furans, ene-yne-ketone, magnetic nano-supported, copper(I) catalyst, cyclization

Introduction

Transition-metal-catalyzed organic transformations are powerful tools for the formation of new carbon-heteroatom and carbon-carbon bonds to construct organic functional molecules from readily available starting materials under mild conditions.[1] Many successful strategies have been developed with a variety of homogeneous metal catalysts.[2] However, these reactions, in general, suffered from the deficits in recovery of homogeneous catalysts, the pollution of environment and the separation of products. The development of heterogeneous catalytic systems[3] that can be efficiently reused is the most efficient routes to avoid and solve these problems. Nanoparticles catalysts have been extensively studied and shown good catalytic activities due to their high surface areas during the last decades.[4] There has been increasing emphasis on the use and development of environmentally friendly solid catalyst systems to maximize resource utilization and decrease waste, especially for environmental health and safety.

Although many heterogeneous catalytic transformations for preparation of functionalized molecules have been developed, the catalyst that can be efficiently reused while keeping the inherent activity of the catalytic center is still far from being solved. In addition, separation and recovery of the catalyst constitutes to be important scaffolds and blocks for synthetic chemistry, which is generally performed by filtration with reduced efficiency. Herein, we hope to develop magnetic nanoparticle-supported catalyst that can be separated from the reaction medium by external permanent magnets for the preparation of furans[5] via domino reaction.

Domino reactions[6] have been developed to enable the rapid construction of complex and diverse furan molecules starting from simple substrates. What's more, they have increased synthetic efficiency by obviating the isolation and purification of intermediates, decreasing the number of laboratory operations required and the quantities of chemicals and solvents used. Recently, transition-metals are widely used for the formation of furan derivatives, such as Pd,[7] Cu,[8] Au,[9] and Ag.[10] Although a range of domino reactions have been developed to prepare the furans, the development of magnetic nanoparticle is still highly favorable for the construction of furans.

Experimental

General

Transmission electromicroscopy (TEM) was performed at the research resources center of South China Normal University, with a JEM-2100HR microscope operating at an accelerating voltage of 100—200 kV. The samples were dispersed in high-purity ethanol under sonication, after which a carbon-coated 400 mesh copper grid was immersed in the suspension and then air-dried. A slight aggregation of the nanoparticles was observed due to magnetic interactions with the electron beam. Powder X-ray diffraction (XRD) measurements were performed at room temperature over the range

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$2\theta = 15° - 80°$ with a BRUKER D8 ADVANCE diffractometer. Fourier transform IR (FTIR) spectra were collected with a BRUKER FT/IR-460 Plus spectrophotometer in the 450—4000 cm^{-1} range. The spectra of the samples were obtained in KBr pellets (Merck, spectroscopic grade) containing 1 wt% MNPs. ^1H NMR spectra and ^{13}C NMR spectra were recorded using a Bruker Avance 400 MHz NMR spectrometer (100 MHz for carbon) and respectively referenced to δ 7.26 and 77.0 for chloroform-*d* solvent with TMS as internal standard. Mass spectra were recorded on a Shimadzu GCMS-QP5050A at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m). TLC was performed using commercially prepared 100—400 mesh silica gel plates (GF_{254}), and visualization was effected at 254 nm.

Synthesis of catalysts

Synthesis of Fe_3O_4 MNPs In the case of ammonia water or diethylamine syntheses, 20 mmol of $FeCl_3 \cdot 6H_2O$ and 10 mmol of $FeCl_2 \cdot 4H_2O$ were dissolved in 25 mL of deoxygenated 0.5 mol/L HCl solution. This solution was quickly added to 250 mL of a deoxygenated 3.0 mol/L solution of ammonia water or diethylamine at r.t. with vigorous mechanical stirring under an argon atmosphere. A black precipitate formed immediately, and stirring was continued for 2 h at that temperature under an argon atmosphere. After that time, the black precipitate was magnetically separated, washed with deoxygenated water several times, and stored in 0.1 mol/L TMAOH for future use. A similar procedure was followed for the synthesis of Fe_3O_4 with the inorganic base NaOH (pH 14).

Synthesis of $Cu_2O@Fe_3O_4$ MNPs In the case of the syntheses with ammonia water or diethylamine, 5 mmol of $Cu_2Cl_2 \cdot 6H_2O$ was dissolved in a solution of 1 mL of 37% HCl in 4 mL of water, and 20 mmol of $FeCl_3 \cdot 6H_2O$ and 10 mmol of $FeCl_2 \cdot 4H_2O$ were dissolved in 40 mL of water. The two solutions were mixed at r.t., and then quickly added to 200 mL of 3.0 mol/L ammonia water or diethylamine at 85 ℃ with vigorous mechanical stirring under an argon atmosphere. A brownish black precipitate formed immediately, and stirring was continued for 2 h at 85 ℃. After that time, the reaction mixture was cooled to room temperature, and the precipitate ($Cu_2O@Fe_3O_4$ MNPs) was magnetically separated, washed with water several times, and dispersed in 0.1 mol/L TMAOH. For comparison, the nanomaterials were also prepared using aqueous NaOH solution (pH 14) under the same experimental conditions.

Synthesis of 2a according to the following procedure 3-(Oct-2-ynylidene)pentane-2,4-dione (0.5 mmol), 5 mmol% *L*-proline and 5 mol% $Cu_2O@Fe_3O_4$ were stirred for 12 h in THF (3 mL) at r.t. After completion of the reaction (monitored by TLC), the catalyst could be easily separated by an external permanent magnets. And then the solvent was removed and the crude product was separated by column chromatography [eluted with *V*(petroleum ether) : *V*(ethyl acetate) = 6 : 1] to give a pure sample of **2a**.

Synthesis of 3a according to the following procedure 3-(Oct-2-ynylidene)pentane-2,4-dione (0.5 mmol), 1 mol% *L*-proline, 5 mol% $Cu_2O@Fe_3O_4$ and THF (3 mL) were stirred for 12 h in a closed system under protection of purified argon at r.t. After completion of the reaction (monitored by TLC), the catalyst could be easily separated by external permanent magnets. And then the solvent was removed and the crude product was separated by column chromatography (eluted with *V*(petroleum ether) : *V*(ethyl acetate) = 12 : 1) to give a pure sample of **3a**.

Results and Discussion

At the outset of our studies, 3-(oct-2-ynylidene)-pentane-2,4-dione **1a** was chosen as model substrates to optimize the suitable reaction conditions and the results are summarized in Table 1. A variety of nano-copper(I) catalyst, solvents, additives, oxidant, temperatures and time were screened. Various nanoparticle-supported catalysts, such as $Cu_2O@Fe_3O_4$, $CuBr@Fe_3O_4$, $CuCl@Fe_3O_4$, $CuO@Fe_3O_4$ and nano-Cu_2O, were firstly tested by using air as oxidant in THF at room temperature for 12 h (Table 1, Entries 1—5). The results showed that the product **2a** was formed in 45% yield in the presence of $Cu_2O@Fe_3O_4$. Other catalysts also generated **2a** in 10%—42% yields. Notably, the side product **3a** was also detected. We next hope to optimize the suitable conditions for the formation of **2a** and **3a** respectively in good yields. Among solvents surveyed, the moderate yield of **2a** was formed in CH_3CN, CH_2Cl_2, CH_3OH, DMSO and DMF (Table 1 Entries 6—10). And it was indicated that THF was the most effective media for this domino reaction. Subsequently, additives were examined (Table 1 Entries 11—13) and the results indicated that higher yield of **2a** was obtained by using *L*-proline as additive (Table 1 Entry 13). We next tried to improve the yields of **2a** by using oxygen with increasing oxygen pressure. The results indicated that the products were formed in 82%, 73% yields by using 1 atm and 2 atm of O_2 respectively (Table 1, Entries 14, 15). To our delight, the products **2a** and **3a** were formed in 10% and 79% yields respectively in the protection of N_2 (Table 1, Entry 16). The good yield was obtained in the protection of Ar (Table 1, Entry 17). The formation of $Cu_2O@Fe_3O_4$ was confirmed by TEM (Figure 1a) and XRD (Figure 2).

Having in hand a highly efficient catalytic system, we then investigated the scope of the reaction for cyclization of ene-yne-ketone to synthesize 2-carbonyl furans (Table 2). First, alkyl-substituted alkyne ($R = CH_3(CH_2)_4$) was examined for this domino process. We were pleased to find that this cyclization/oxidation sequence tolerated a wide range of group on the carbonyl carbon (R^1, R^2). Different substituted substrates, such as $R^1 = CH_3$, $ClCH_2$; $R^2 = CH_3$, CH_3O, $(CH_3)_3CO$, EtO,

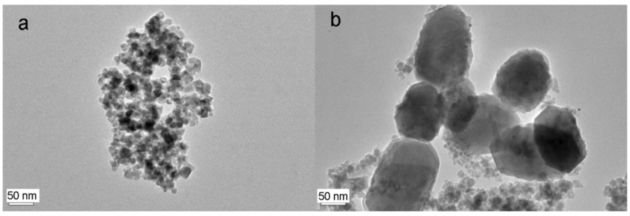


Figure 1 TEM images of $Cu_2O@Fe_3O_4$ before reaction (a) and after reuse eight times (b).

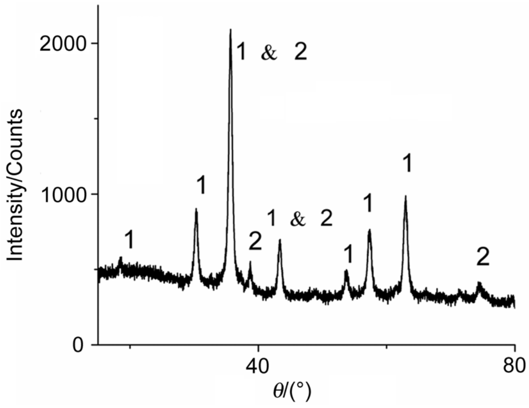


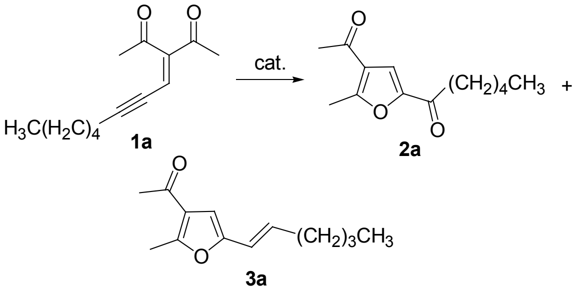
Figure 2 XRD pattern of $Cu_2O@Fe_3O_4$.

p-ClPhNH, *o*-CH_3OPhNH led to a beneficial effect on the reaction outcome, and in most cases the corresponding products (**2a**—**2k**) were obtained in good yields. Commercially available cyclic 1,3-dicarbonyl compounds were next tested to explore the scope of this transformation. To our delight, the results indicated that the reaction would be successfully extended to cyclic 1,3-dicarbonyl compounds under the optimum conditions and afforded the corresponding products in good yields.

For further investigation, phenyl-substituted alkyne (R=Ph) was also employed for this $Cu_2O@Fe_3O_4$ catalyzed domino reaction (Table 2). It was pleased to find that this cyclization/oxidation sequence also tolerated a wide range of group on the carbonyl carbon (R^1, R^2). These results indicated that this transformation was applicable to both open and cyclic 1,3-dicarbonyl compounds and the desired products were formed in good yields. Interestingly, the group (R^2 = *p*-ClPhNH, *c*-CH_3OPhNH) led to a beneficial effect on the reaction outcome, and the corresponding products were obtained in good yields. All these results demonstrated that this domino reaction could occur with functional groups at different positions of the alkyne terminus and carbonyl carbon. It was worthy to note that all of the desired products were formed with high regioselectivity.

We next explored the scope of this remarkable transformation for synthesis of 2-vinyl furans (Table 3). This reaction was compatible with a variety of functional groups (R^1, R^2), including methyl, ester, cycloalkyl, and carboxamide and gave the corresponding products **3a**—**3k** in 41%—87% yields. Notably, the ester, cycloalkyl and carboxamide groups remained unaffected under these reaction conditions. The method indeed was nice, especially as vinylfurans were not easy to obtain.

Table 1 Optimization of reaction conditions[a]



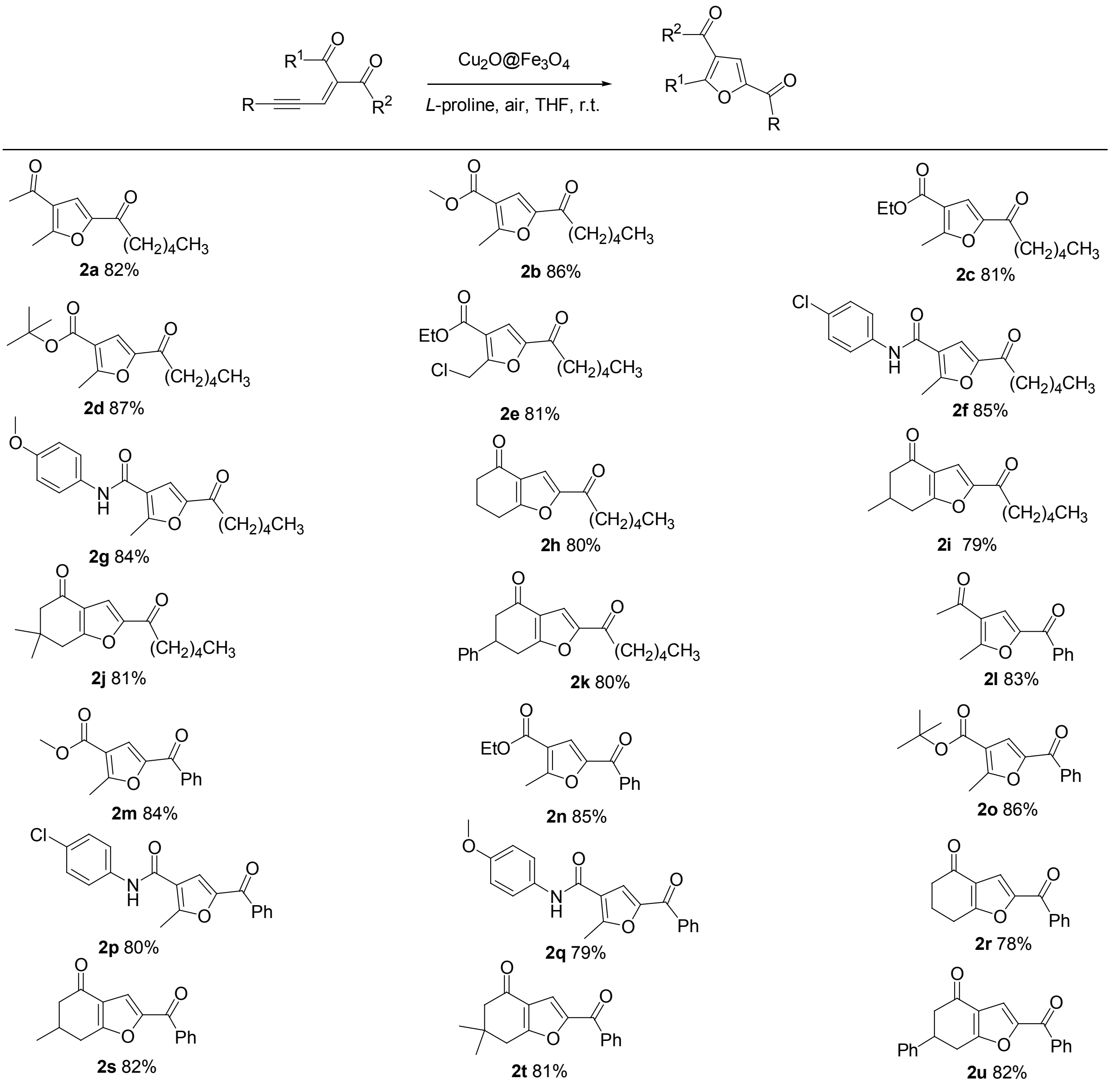
Entry	Catalyst	Solvent	Additive	Oxidant	Yield[b]/%	
					2a	**3a**
1	$Cu_2O@Fe_3O_4$	THF	—	Air	45	trace
2	$CuBr@Fe_3O_4$	THF	—	Air	42	<5
3	$CuCl@Fe_3O_4$	THF		Air	23	
4	$CuO@Fe_3O_4$	THF	—	Air	10	<5
5	nano-Cu_2O	THF	—	Air	30	<5
6	$Cu_2O@Fe_3O_4$	CH_3CN	—	Air	26	<5
7	$Cu_2O@Fe_3O_4$	CH_2Cl_2	—	Air	24	<5
8	$Cu_2O@Fe_3O_4$	CH_3OH	—	Air	31	—
9	$Cu_2O@Fe_3O_4$	DMF	—	Air	35	trace
10	$Cu_2O@Fe_3O_4$	DMSO		Air	38	trace
11	$Cu_2O@Fe_3O_4$	THF	CH_3CO_2H	Air	26	<5
12	$Cu_2O@Fe_3O_4$	THF	$PhCO_2H$	Air	22	<5
13	$Cu_2O@Fe_3O_4$	THF	*L*-proline	Air	88	<5
14	$Cu_2O@Fe_3O_4$	THF	*L*-proline	O_2 (1 atm)	82	trace
15	$Cu_2O@Fe_3O_4$	THF	*L*-proline	O_2 (2 atm)	73	trace
16	$Cu_2O@Fe_3O_4$	THF	*L*-proline	N_2	10	79
17[c]	$Cu_2O@Fe_3O_4$	THF	*L*-proline	Ar	<5	89

[a] Reaction conditions: **1a** (0.5 mmol), catalyst (5 mol%), additive (1 mol%), r.t., solvent (2.0 mL), 12 h. [b] GC Yields. [c] The reaction was performed in a closed system under protection of purified argon.

Finally, we turned our attention to reusability of catalyst. It was found that catalyst could be recovered by using external magnets, with high efficiency and up to 99% recovery of catalyst. After completion of the reaction, the mixture turned clear and catalyst was deposited on the magnetic bar within 30 s, and then re-used in the next reaction (Figure 3). Noteworthily, 72% yield was maintained even when the catalyst was reused for 8 times.

The most plausible Cu(I)-catalyzed reaction mechanism for cyclization/oxidation ofene-yne-ketone has been depicted in Scheme 1. The substrates **1a** coordinated with Cu(I) species to form the metal complexes **A**. Subsequently, an intramolecular 5-exo-dig cyclization by nucleophilic attack of the oxygen of carbonyl onto

Table 2 $Cu_2O@Fe_3O_4$-catalyzed synthesis of 2-carbonyl furans



Isolated yields.

Scheme 1 Proposal mechanism

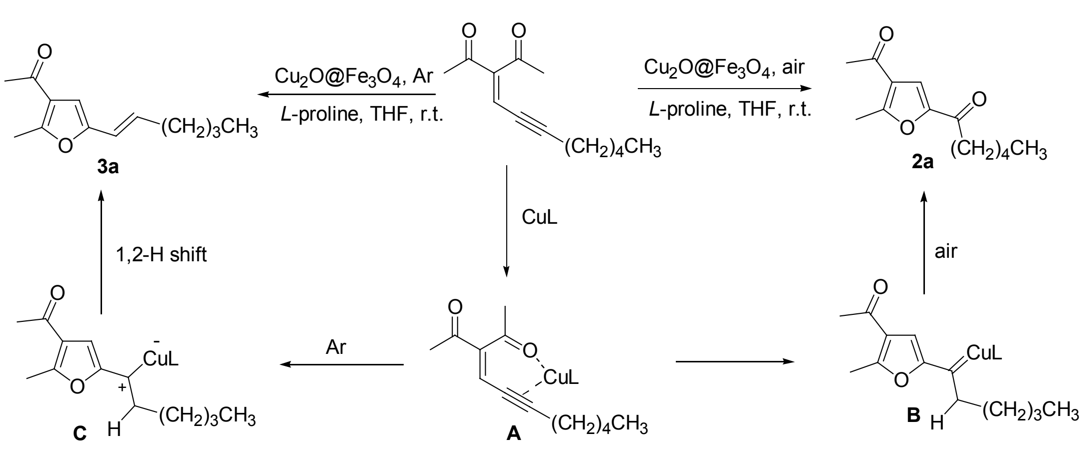
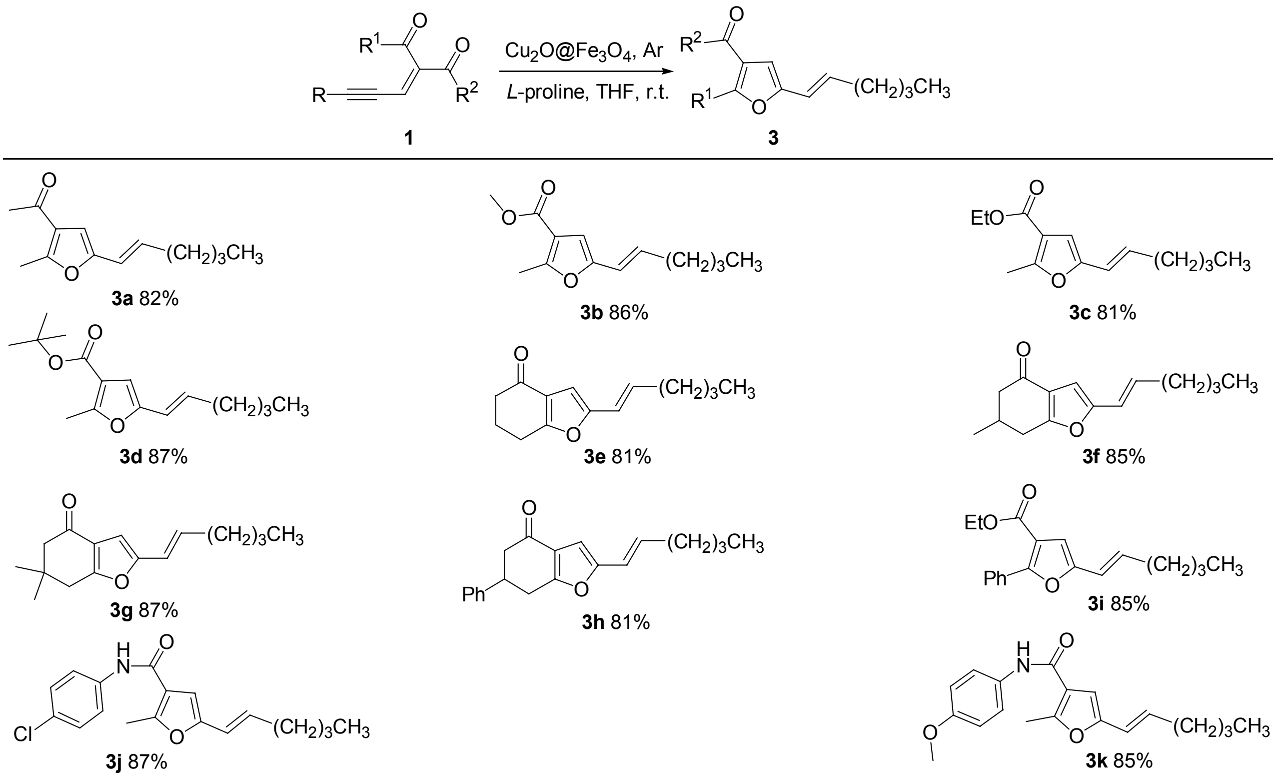


Table 3 $Cu_2O@Fe_3O_4$-catalyzed synthesis of 2-vinyl furans



Isolated yields.

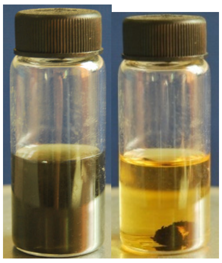


Figure 3 Photographs showing the separation of catalyst.

the carbon atom of alkyne has taken place to generate the (2-furyl)carbene complex **B** and zwitterionic intermediate **C**, respectively. The copper carbene complex **B** underwent carbene-oxidation with air to give the corresponding product **2a** and release the copper catalyst. While the desired product **3a** was formed via 1,2-H migrations of intermediate **C** and copper catalyst was released.

Conclusions

In conclusion, we have developed an efficient $Cu_2O@Fe_3O_4$-catalyzed domino reaction that proceeds through a cyclization of ene-yne-ketone. The reaction provides a convergent approach to form carbon-oxygen bond and carbon-oxygen double bond for construction of furan derivatives with good yields. It represents a facile synthetic route and the eco-friendly catalyst can be easily separated by magnetic adsorption and reused. Further studies will focus on cyclization of ene-yne compounds and synthetic applications of this reaction are being carried out in our laboratory.

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