Amidoxime fibers-copper-catalyzed cross-dehydrogenative coupling of N,N-dimethylanilines and aromatic terminal alkynes

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Abstract

A heterogeneous Cu(II)-AOFs catalyst, Cu(II) supported on amidoxime fibers (AOFs), is successfully applied to the cross-dehydrogenative coupling of aromatic terminal alkynes and N,N-dimethylanilines to form propargylamines. The Cu(II)-AOFs catalyst shows high catalytic activity with the yields of the corresponding propargylamines reaching 90% at 70 °C for 4 h without the protection of an inert gas. The Cu(II)-AOFs coordinate with the imine ion intermediate generated during the reaction, making the coupling facile. X-ray photoelectron spectrometer, scanning electron microscope, and energy dispersive X-ray spectroscopy results show that Cu(II) successfully coordinates with N and O atoms on the surface of the fibers with the mutual conversion between monovalent and divalent Cu in the Cu-AOFs being the catalytically active center. The catalyst can be recycled more than four times, and the catalytic activity is not obviously reduced. This process represents a new pathway for the formation of propargylamines using a Cu(II)-AOFs catalyst.

Keywords

amidoxime fibers, cross-dehydrogenative coupling reaction, Cu(II)-AOFs, heterogeneous catalyst, recycling

Introduction

Propargylamines, are the components of many bioactive intermediates,1 and are widely used for the preparation of nitrogen-containing compounds, such as pyrazines, oxazoles, and pyroles.2 The preparation of propargylamines has attracted interest in the fields of medicinal chemistry and organic synthesis.3,4 Traditional synthetic methods toward propargylamines are reactions of propargyl halides with amines and functional amines with metal acetylides and the one-pot, three component reactions of aldehydes/dihalomethanes, amines, and alkynes.5 However, these methods generally require a leaving functional group or pre-functionalized aldehydes and amines.

Recently, numerous cross-dehydrogenative coupling (CDC) methods have attracted significant interest via transition-metal activation of the sp³C–H bond adjacent to a nitrogen atom to form directly the propargylamines. In 2004, it was first reported that CuBr catalyzed the synthesis of propargylamines from anilines and terminal alkynes in the presence of tert-butyl hydroperoxide (TBHP), and the yields of 12%–82% were obtained at 100 °C in 3 h.6 When (t-BuO)₂ is used as the oxidant, FeCl₃ can catalyze the coupling reaction of tertiary amines with terminal alkynes.7 It has been reported that a Cu(acac)₂ catalyst promoted the reaction of tertiary amine oxide with terminal alkynes at 110 °C under an N₂ atmosphere and provided 53%–89% yields of the corresponding propargylamines.8 The reaction of N-phenyltetrahydroisoquinoline with phenylacetylene was realized with a dual catalyst composed of the photooxidation catalyst [Ru(bpy)₂(dtbbpy)](PF₆)₂ and the metal salt (MeCN)₄CuPF₆, with the desired product being obtained in 84% yield under visible light over 16 h.9 Other copper-catalyzed methods for the synthesis of propargylamines have also been developed by several research groups.10,11 However, most of the above CDC reactions involve...
homogeneous catalysts, which are difficult to recover and separate after the reaction. In order to solve these problems, various heterogeneous catalysts have been developed and applied in CDC experiments. For example, using Y-type zeolite-supported copper nanoparticles (CuNPs/ZY) as the catalyst led to the successful reaction between anilines and terminal alkynes to obtain the desired products in moderate to excellent yields at 70 °C over 20 h.12 The ZnBr2 and manganese oxide–based octahedral molecular sieves composite catalyst (Zn2+–OMS-2) promoted the CDC reaction of aliphatic amines and terminal alkynes, and when cyclopentyl methyl ether (CPME) was used as the solvent and oxygen as the oxidant, the yields of the corresponding products were 13%–83% at 100 °C over 8 h.13 A metal-organic framework catalyst, MOF-199, was used to catalyze the alkynylation reaction of N,N-dimethylaniline and phenylacetylene in 79% yield at 120 °C over 3 h.14 In addition, the nanocatalyst Cu6Se4.5NPs was applied in the reaction of N,N-dimethylbenzylamine and phenylacetylene, and the desired product was obtained in 62% yield at 100 °C in 3 h in the presence of N2.15 Later, copper(I) ligated with 4,5-bis[(phenylthio/seleno)methyl]acridine catalysis was reported to catalyze the same reaction of N,N-dimethylbenzylamine and phenylacetylene to afford a 73% isolated yield of the products at 60 °C over 6 h under inert gas protection.16 However, after reaction with a Zn2+-OMS-2 catalyst, only OMS-2 molecular sieves were recovered, which needed to be reloaded by adding ZnBr2 for the next experiment. The process for the preparation of the nanocatalyst is not only lengthy and complicated but also needs a harsh environment without water or oxygen. In addition, flammable and explosive lithium powder or easily oxidized trioctylphosphine is indispensable experimental materials in the preparation of such systems.

In this research, we prepared a metal cation–supported amidoxime fiber (AOFs) catalyst using cheap raw materials via a simple preparative method. The catalyst demonstrated good performance CDC reactions of N,N-dimethylanilines and terminal alkynes. The AOFs (involving [H2N–C=N–OH] side chain group) with abundant and coordinating –NH2, –OH functional groups, were obtained by modifying the –C≡N functional group in the polyacrylonitrile (PAN) fiber with NH2OH. When the AOFs were reacted with copper bromide solution at room temperature, the N and O atoms on the surface of the AOFs, which have lone pairs of electrons, can coordinate with the empty orbitals of Cu(II) to give Cu(II)-AOFs. The Cu(II)-AOFs catalyst shows high catalytic activity and selectivity for the CDC reaction of N,N-dimethylaniline and phenylacetylene to form the propargylamine at 70 °C over 4 h in air. The coupling product is obtained in 90% yield, and the alkene selectively couples with a methyl group of the N,N-dimethylaniline. In addition, the Cu(II)-AOFs is an effective and reusable heterogeneous catalyst for the CDC reaction.

Results and discussion

Analysis of scanning electron microscope and energy-dispersive X-ray for the Cu-AOFs

The morphology of the Cu(II)-AOFs before the reaction was characterized by scanning electron microscope (SEM). As shown in Figure 1(a), the surface of the Cu(II)-AOFs before the reaction was very smooth, the energy-dispersive X-ray (EDX) analysis (Figure 1(b)) revealed the presence of a large amount of Cu in the Cu-AOFs catalyst.

Analysis of X-ray photoelectron spectrometer for the Cu-AOFs

In order to clarify the change of the valence state of the copper during the reaction, X-ray photoelectron spectrometer (XPS) measurements of the Cu-AOFs before and after the reaction were carried out. The XPS of Cu(II)-AOFs before reaction showed that the catalyst was composed of five elements: C, N, O, Cu, and Br, as shown in Figure 2(a). Figure 2(b) shows that there is only one valence state of Cu(II) in the Cu(II)-AOFs before the reaction, showing one peak at 933.11 eV.17 However, the copper was found to exist in two different valence states in the Cu-AOFs after the reaction. As shown in Figure 2(c), the peak at 934.48 eV is due to Cu(II) 2p3/2 and the peak at 932.42 eV is attributed to Cu(I) 2p3/2,18 which can also be proved by the CuL3M45M45 Auger spectroscopy binding energy located at 571 eV (see the Supporting Information).19 Subsequently, the reacted Cu-AOFs were placed in air at room temperature for 1 week and then studied again by XPS. The results are shown in Figure 2(d). Unexpectedly, the peak intensity of Cu(II) becomes
higher and the peak intensity of Cu(I) becomes lower, which suggests that Cu(I) in the Cu-AOFs is unstable, and most are oxidized to Cu(II) by air. Therefore, the above XPS data indicate there may be a mutual conversion between monovalent and divalent Cu during the Cu-AOFs catalytic reaction. At the same time, this feature shows promise for the reuse of the catalyst. Figure 2(e) and (f) show the characteristic lines of N and O. As shown in Figure 2(e), the peaks due to N1s in the AOFs appear at 399.08 and 399.75 eV, respectively. However, the two peaks of N1s increased to 399.52 and 400.56 eV in Cu(II)-AOFs. The increase of binding energy is mainly due to the combination of Cu(II) and N atoms in Cu(II)-AOFs forming a N–Cu bond. The binding energies at 531.42 and 532.61 eV shown in Figure 2(f) are the characteristic of O1s in AOFs. Compared with the binding energies of O1s in Cu(II)-AOFs, these two peaks are changed to 531.97 and 532.99 eV, respectively, which are ascribed to the O–Cu bond between Cu(II) and O atoms. In summary, the above results prove Cu(II) has successfully coordinated with the AOFs during preparation of the catalyst.

**Optimization of the reaction conditions**

In order to obtain high yields, the conditions for the reaction of N,N-dimethylaniline with phenylacetylene were optimized. As shown in Table 1, the desired coupling product is not obtained in the absence of copper catalyst (entry 1). The catalytic efficiency of AOFs supported on copper was higher than that of AOFs supported on Pd, Fe, and Ni (entries 5, 9, 10, and 11). Compared with fibers loaded with copper(II) chloride and copper(II) acetate, the fiber loaded with copper(II) bromide gave the product in 90% (entries 3–5). The difference in yields may be related to the Ksp of the Cu(I) substance. Because the Ksp of copper(I) bromide...
Table 1. Optimization of the reaction conditions. 

| Entry | Catalyst     | Solvent | Temperature (°C) | Yield (%)b |
|-------|--------------|---------|-----------------|------------|
| 1     | No catalyst  | DCE     | 70              | 0          |
| 2     | CuBr2        | DCE     | 70              | 78c        |
| 3     | Cu(II)-AOFs  | DCE     | 70              | 75a        |
| 4     | Cu(II)-AOFs  | DCE     | 70              | 49a        |
| 5     | Cu(II)-AOFs  | DCE     | 70              | 90a        |
| 6     | Cu(II)-AOFs  | DCE     | 70              | 62a        |
| 7     | Cu(II)-AOFs  | DCE     | 70              | 83a        |
| 8     | Cu(II)-AOFs  | DCE     | 70              | 90a        |
| 9     | Cu(II)-AOFs  | DCE     | 70              | 15         |
| 10    | Fe(III)-AOFs | DCE     | 70              | 39         |
| 11    | Ni(II)-AOFs  | DCE     | 70              | 22         |
| 12    | Cu(II)-AOFs  | THF     | 60              | 18         |
| 13    | Cu(II)-AOFs  | dioxane | 70              | 83         |
| 14    | Cu(II)-AOFs  | DMF     | 70              | 73         |
| 15    | Cu(II)-AOFs  | DMSO    | 70              | 74         |
| 16    | Cu(II)-AOFs  | H2O     | 70              | 47         |
| 17    | Cu(II)-AOFs  | DCE     | 60              | 70         |
| 18    | Cu(II)-AOFs  | DCE     | 80              | 87         |
| 19    | Cu(II)-AOFs  | DCE     | 70              | 37c        |

*aReaction conditions: N,N-dimethylaniline (1 mmol), phenylacetylene (1.3 mmol), TBHP (1 mmol), solvent (2 mL), Cu(II)-AOFs (Cu(II): 4.41 mol%, 0.0764 g), and reaction time (4 h).*  
*bYield determined by GLC.*  
*cOnly copper(II) bromide was used as the catalyst without AOFs.*  
*dCopper(II) chloride.*  
*eCopper(II) acetate.*  
*fCu(II)-AOFs (Cu(II): 2.21 mol%, 0.0383 g).*  
*gCu(II)-AOFs (Cu(II): 3.53 mol%, 0.0612 g).*  
*hCu(II)-AOFs (Cu(II): 8.83 mol%, 0.1530 g).*  
*iCu(II)-AOFs DCE 70 90i*  
*jTBHP (1 mmol), solvent (2 mL), Cu(II)-AOFs (Cu(II): 4.41 mol%, 0.0764 g), and reaction time (4 h).*  
*kDCE prove to be the best solvent (entry 1).*  
*lCu(II)-AOFs DCE 70 90d*  
*mCu(II)-AOFs DCE 70 90e*  
*nCu(II)-AOFs DCE 70 90f*  
*oCu(II)-AOFs DCE 70 90g*  
*pCu(II)-AOFs DCE 70 90h*  
*qCu(II)-AOFs DCE 70 90i*  
*rCu(II)-AOFs DCE 70 90j*  
*sCu(II)-AOFs DCE 70 90k*  
*tCu(II)-AOFs DCE 70 90l*  
*uCu(II)-AOFs DCE 70 90m*  
*vCu(II)-AOFs DCE 70 90n*  
*wCu(II)-AOFs DCE 70 90o*  
*xCu(II)-AOFs DCE 70 90p*  
*yCu(II)-AOFs DCE 70 90q*  
*zCu(II)-AOFs DCE 70 90r*  
| Entry | Catalyst     | Solvent | Temperature (°C) | Yield (%)b |
|-------|--------------|---------|-----------------|------------|
| 18    | Cu(II)-AOFs  | DCE     | 70              | 87         |
| 19    | Cu(II)-AOFs  | DCE     | 70              | 37c        |

The effect of substituent groups on the catalytic performance

Under the above reaction conditions, the effect of different substituents on the catalytic performance of Cu(II)-AOFs was also studied. As shown in Table 2, the properties and steric effects of the substituents had no significant influence on the reaction, and good yields of the desired coupling products were obtained. These results indicate that the Cu(II)-AOFs catalyst has good substrate adaptability for the coupling reaction of N,N-dimethylaniline and aromatic alkyne derivatives.

Reuse of the Cu(II)-AOFs catalyst

In order to further explore the catalytic performance of the Cu(II)-AOFs in this reaction, the reuse of the catalyst was tested and the results are shown in Figure 3. It can be seen the Cu(II)-AOFs can be reused at least four times without a significant decrease in activity. In order to explore the nature of the catalyst, we conducted a hot filtration experiment. Under the optimized reaction conditions, the Cu(II)-AOFs catalyst was used to catalyze the reaction of phenylacetylene and N,N-dimethylaniline. When the product was present in 30% yield after 0.5 h, the Cu(II)-AOFs were separated by hot filtration, and the filtrate was reacted at 70 °C for 3.5 h. The experimental results showed that the yield of product was not further improved. Combined with the efficiency of reuse, this proved that there is only a small amount of copper dissolved in the reaction solution.

Exploration of the experimental mechanism

Based on the above catalytic performance and catalyst characterization analysis, we have proposed a possible mechanism for the Cu(II)-AOFs-catalyzed dehydrogenative coupling of N,N-dimethylaniline and phenylacetylene (Scheme 1). First, the N,N-dimethylanilines react with Cu(II)-AOFs through a redox reaction to form N,N-dimethylanilines radical cation A and Cu(I)-AOFs,12 and TBHP oxidizes the Cu(I)-AOFs to Cu(II)-AOFs (achieving Cu(I) and Cu(II) cycles), and simultaneously generates t-BuO and OH·. Next, through deprotonation and single-electron transfer, t-BuO and amine radical cation A generate an imine intermediate, which can coordinate with the Cu(II)-AOFs to form intermediate B.10 At the same time, the aromatic terminal alkyne is coordinated to the Cu(I)-AOFs and so activated toward deprotonation to produce aromatic copper acetylide C. Finally, the coupling product is obtained by the nucleophilic reaction between imine intermediate B and the copper acetylide C.
Conclusion

In summary, Cu(II)-AOFs show excellent catalytic performance for the CDC reaction of N,N-dimethylanilines and aromatic terminal alkynes to form propynylamines, and the desired product can be obtained in 90% yield in air at 70 °C over 4 h. Importantly, by simple filtration and recovery after reaction, the catalyst can be reused at least four times. SEM and XPS characterization proved that the Cu(I)/Cu(II)-AOFs redox behavior of the catalyst is the key to the reaction cycle. This research provides a new pathway for the CDC reaction for the synthesis of propargylamines using a heterogeneous catalyst.

Experimental section

Reagents and characterization

PAN was purchased from Anqing Carbon Co., Ltd., China. Reagents were provided by Sinopharm Chemical Reagent Co., Ltd., China, and were not purified further. The morphology and elemental analysis of the catalyst Cu(II)-AOFs were established using a Hitachi S-4800, Japan field-emission SEM and EDX. The element valence states on the surface of Cu-AOFs were characterized using a Thermo Fisher Scientific.
ESCALAB 250 XPS, USA. Infrared spectra (IR) were recorded on a Perten DA 7200, Sweden spectrometer with KBr films. High-resolution mass spectra (HRMS) were obtained on an Agilent, USA mass spectrometer. The Cu content in the Cu(II)-AOFs catalyst was measured using an Inductively Coupled Plasma Optical Emission Spectrometer (ICP-OES), Varian 710-ES, USA. A Bruker ARX-400, Germany nuclear magnetic resonance spectrometer was used to obtain the 1H NMR, 13C NMR, and 19F NMR for fluorine-containing products spectra of the reaction products.

**Preparation of Cu(II)-AOFs**

The Cu(II)-AOFs catalyst is prepared as follows.20 PAN fibers (5 g) were added to a pre-prepared hydroxylamine aqueous solution (1 mol L⁻¹, 250 mL), and the reaction was stirred in a water bath at 65 °C. After 1.5 h, the fibers were filtered, washed with distilled water to neutrality, and dried naturally to afford the AOFs (5 g). Finally, the AOFs were added copper(II) bromide solution (0.1 mol L⁻¹, 10 mL) at 45 °C for 2 h to give a fiber-supported Cu(II) catalyst (Cu(II)-AOFs). The Cu(II)-AOFs were filtered, washed with distilled water and ethyl acetate, and dried at 45 °C to obtain the green Cu(II)-AOFs. The Cu content in Cu(II)-AOFs was 3.67 wt% according to inductively coupled plasma optical emission spectrometer (ICP-OES) analysis. Scheme 2 shows the synthesis of the Cu(II)-AOFs catalyst.

**General procedure for the CDC reaction**

At room temperature, Cu(II)-AOFs (Cu(II): 4.41 mol%, 0.0764 g) was added to a solution of terminal alkynes 2 (1.3 mmol), N,N-dimethylanilines 1 (1 mmol) and TBHP (1 mmol) in DCE (2 mL). The resulting mixture was vigorously stirred in an oil bath at 70 °C for 4 h. After cooling to room temperature, the Cu(II)-AOFs catalyst was separated by filtration, and then washed with ethyl acetate and distilled water. Finally, the washed catalyst was dried for half an hour at 50 °C and reused in the next experiment. The reaction mixture was extracted three times with ethyl acetate and the combined organics were dried over anhydrous magnesium sulfate and concentrated by rotary evaporation to remove the solvent. The residue was purified by the silica gel column chromatography (eluent:petroleum ether/ethyl acetate = 50:1) to afford the final coupling product. As for known coupling products, only 1H NMR and 13C NMR spectra were confirmed with previously reported literature, and the new compounds were characterized by 1H NMR, 13C NMR spectra, IR, and mass spectra.

**Declaration of conflicting interests**

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**Supporting information**

The characterization of other coupling products and the CuL₃M₄5M₄5 Auger spectroscopy of Cu-AOFs are shown in Supporting Information.

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Supplemental material

Supplemental material for this article is available online.

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