Ligand-free catalytic system for the synthesis of diarylethers over Cu₂O/Cu-CNTs as heterogeneous reusable catalyst

Ying-Peng Zhang *, Ya-Cong Jiao, Yun-Shang Yang *, Chun-Lei Li

School of Petrochemical Engineering, Lanzhou University of Technology, Lanzhou 730050, China

ABSTRACT

Various substituted diarylether derivatives were prepared by using heterogeneous reusable Cu₂O- and Cu-coated carbon nanotubes (Cu₂O/Cu-CNTs) as catalyst under ligand-free conditions, which provided good to excellent yields. The catalyst was characterized by TEM, XRD, and AAS analysis. The effects of solvent, base, and amount of catalyst for the O-arylation were investigated. The catalyst could be recovered by simple filtration from the reaction mixture without further treatment and reused several times with consistent catalytic activity. In addition, CNTs could also be recovered from the used Cu₂O/Cu-CNTs by a simple acid treatment.

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Diarylethers are key moieties in many biologically active natural products.[1] The total synthesis of many natural cyclopeptides, such as vancomycin and anti-HIV agents like chloropeptin, which contain this substructure, has received considerable attention.[2] Transitional metal-mediated Ullmann-type reactions of phenols and aryl halides are the most general way to prepare diarylethers.[3] Palladium[4] and copper[5] catalysts have so far been the metals of choice for such purposes. Despite the high efficiency of the Pd-catalyzed methods, the use of expensive palladium and elaborate phosphorated ligands would limit its applications to large- or industrial-scale production.[6]

Cu-catalyzed Ullmann coupling between an aryl halide and phenol is a viable alternative to Pd-catalyzed diarylether synthesis. However, traditional copper-mediated Ullmann-type coupling often needs harsh reaction conditions, such as high reaction temperature, stoichiometric amounts of copper, with only low to moderate yields, which limited its application on industrial-scale synthesis. Therefore, considerable efforts have been devoted in the past few decades to the development of new methods for the preparation of diarylethers under relatively mild conditions. Recently, major progress has been made in modifying the Cu-catalyzed Ullmann coupling reaction by using several special ligands[7] and heterogeneous reusable catalysts.[8] Despite significant progress in the heterogeneous reusable copper-catalyzed O-arylation reac-
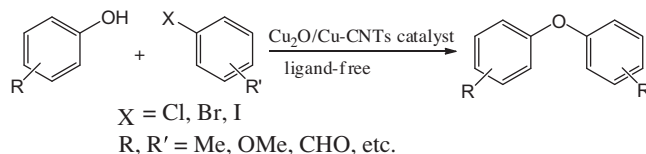
Scheme 1. Cu₂O/Cu-CNTs-catalyzed Ullmann etherification of phenols with aryl halides.

tion, the recovery of catalyst carrier was seldom taken into consideration. On the other hand, carbon nanotubes (CNTs) are widely studied as supports of depositing metal nanoparticles as heterogeneous catalysts due to their extraordinary structure, good electronic conductivity, and improved accessibility of reactants to the active sites.[9] Herein, we report an eco-friendly system for the preparation of diarylethers by using heterogeneous reusable Cu₂O/Cu-CNTs catalyst under ligand-free conditions (Scheme 1). Further, CNTs can also be recovered from the used catalyst by a simple acid treatment.

Cu₂O/Cu-CNTs were prepared by reduction of copper(II) ions in Fehling's reagent.[10] Transmission electron microscopy (TEM) images show that the nanoparticles were coated on the CNTs with the average size of about 15 nm (Fig. 1). The structure of Cu₂O/Cu-CNTs catalyst was determined by powder X-ray diffraction (XRD; Fig. 2). The diffraction pattern of all the peaks match well with the standard XRD patterns (JCPDS 05-0667 and JCPDS 04-0836). Copper content in the catalyst determined by atomic absorption spectrum (AAS) suggests 18 wt.% Cu in the catalyst.

* Corresponding authors. Tel.: +86 1 931 2973644; fax: +86 1 931 2973648.
 E-mail addresses: yingpengzhang@126.com (Y.-P. Zhang), yangguang@lut.cn (Y.-S. Yang).
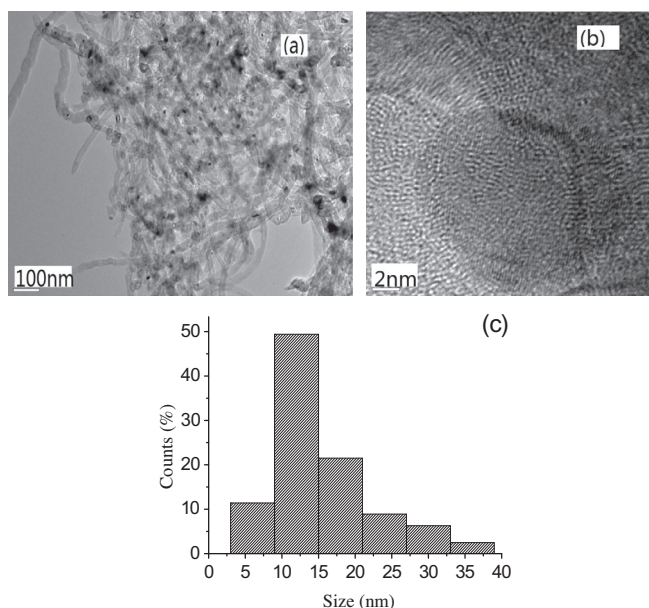
Figure 1. (a) TEM image of Cu₂O/Cu-CNTs; (b) A high-magnification TEM image of Cu₂O/Cu-CNTs; (c) size distribution diagram of Cu₂O/Cu-CNTs.
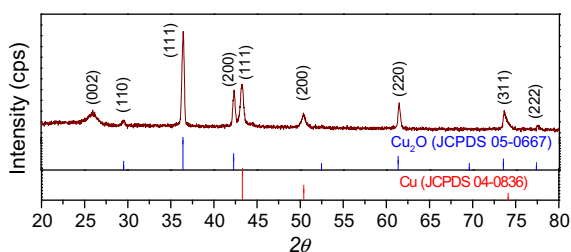

Figure 2. XRD pattern of Cu₂O/Cu-CNTs.

Table 1
Optimization of reaction conditions[a]

Entry	Base	Solvent	Temperature (°C)	Amount of solvent (mL)	Yield[b] (%)
1	Et₃N	NMP	120	10	15
2	Et₃N	DMSO	150	10	12
3	Et₃N	Pyridine	70	10	14
4	Et₃N	CH₃CN	75	10	15
5	Et₃N	CH₃OH	45	10	7
6	Et₃N	DMF	140	10	47
7	NaOMe	DMF	140	10	23
8	KOH	DMF	140	10	24
9	K₃PO₄	DMF	140	10	20
10	K₂CO₃	DMF	140	10	0
11	Cs₂CO₃	DMF	140	10	68
12	Cs₂CO₃	DMF	140	15	76
13	Cs₂CO₃	DMF	140	5	96
14	Cs₂CO₃	DMF	80	5	0
15	Cs₂CO₃	DMF	100	5	0
16	Cs₂CO₃	DMF	120	5	0
17[c]	Cs₂CO₃	DMF	140	5	Trace
18[d]	Cs₂CO₃	DMF	140	5	42
19[e]	Cs₂CO₃	DMF	140	5	0
20[f]	Cs₂CO₃	DMF	140	5	13
21[g]	Cs₂CO₃	DMF	140	5	39

[a] Reaction conditions: phenol (1.0 mmol), bromobenzene (1.2 mmol), base (1.0 mmol), Cu₂O/Cu-CNTs catalyst (0.06 g), 24 h, under nitrogen atmosphere.
[b] Isolated yields.
[c] Reaction for 12 h.
[d] Reaction for 18 h.
[e] Without catalyst.
[f] 10 mol % Cu₂O.
[g] 20 mol % Cu.

To develop the protocol for C–O cross-coupling, the reaction of bromobenzene (1.2 mmol) and phenol (1.0 mmol) catalyzed by Cu₂O/Cu-CNTs (0.06 g) under nitrogen atmosphere was selected as a model reaction to optimize the reaction conditions. In terms of the effect of solvent on the cross-coupling reaction, DMF was found to be the best solvent for the reaction (Table 1, entry 6). Other solvents, including NMP, DMSO, pyridine, and CH₃CN, were less efficient (Table 1, entries 1–4). CH₃OH gave the corresponding product in a 7% yield, which was the worst among these solvents (Table 1, entry 5). Nevertheless, all of these yields were generally low before further optimizations. To increase the efficiency of the coupling reaction, the effects of different bases were investigated (Table 1, entries 6–11). Cs₂CO₃ exhibited the best performance (76%). Et₃N, NaOMe, KOH, and K₃PO₄ gave 47%, 23%, 24%, and 20% yields, respectively. K₂CO₃ showed no activity for this reaction. The reaction was carried out in different amounts of DMF over the range of 5–15 mL (Table 1, entries 11–13). Among different amounts of the solvent, 5 mL of DMF turned out to be the best choice with a yield of 96% (Table 1, entry 13). The amount of catalyst was decreased from 0.08 to 0.02 g and 0.06 g of catalyst was found to be the most effective catalytic system (Fig. 3). At lower temperatures (80, 100 and 120 °C) and shorter reaction times (12 and 18 h), no significant amount of product was formed (Table 1, entries 14–18). The presence of Cu₂O and Cu nanoparticles on

the CNTs led to a significant increase in the yield of C–O cross-coupling (Table 1, entries 13, 20, and 21).

After having optimized the reaction parameters, the scope of the reaction was explored with a range of substituted phenols and aryl halides (Table 2). The presence of a *p*-methyl group or *p*-methoxy group in phenol increased the yield of the coupling reaction (Table 2, entries 2, 10, 16 and 18, and 20). The yield in this coupling reaction decreased when the electron-donating group was present at the *ortho* or *meta* position in phenol (Table 2, entries 3, 4, 6, and 12–14). The steric hindrance of chlorobenzene made no effect on the O-arylation with phenol (Table 2, entries 15 and 19). When reacting with *m*-cresol, bromobenzene bearing an *o*-aldehyde group hindered the cross-coupling reaction (Table 2, entries 3 and 7). The electron-rich chlorobenzene could react with phenol easily and produce a moderate yield (Table 2, entry 17). Iodobenzene and bromobenzene showed the same reactivity when reacting with phenol (Table 2, entries 1 and 11). However, with the effect of steric factors increasing, iodobenzene gradually showed its advantage on the cross-coupling reaction (Table 2, entries 3, 4, 6, and 12–14). *p*-Cresol was successfully coupled with 4-bromobenzaldehyde to give the corresponding diarylether in an excellent yield (Table 2, entry 10). 4-(4-Methoxyphenoxy)benzaldehyde was obtained only in moderate yield compared to 4-(*p*-tolyloxy)benzaldehyde (Table 2, entries 9 and 10).

The reusability of the catalyst in this coupling reaction was also examined using iodobenzene (1.2 mmol) and phenol (1.0 mmol) as substrate in DMF (5 mL) at 140 °C. After the completion of the reaction, the catalyst was filtrated, washed with ethyl acetate (3 × 10 mL), followed by distilled water and ethanol, and then
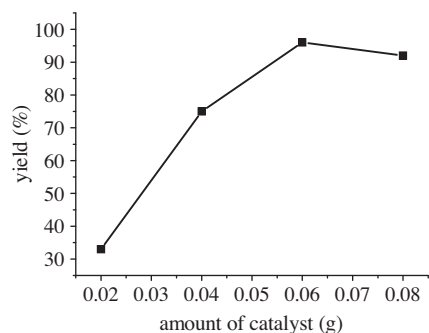
Figure 3. The effect of catalyst amount on the O-arylation reaction of bromobenzene and phenol.

dried under reduced pressure for the usage of the first cycle. Two more cycles were carried out with the same procedure described above and no significant loss of catalytic activity was observed (Table 3).
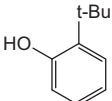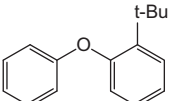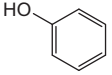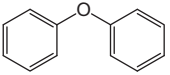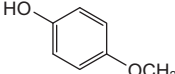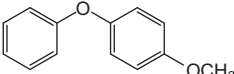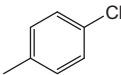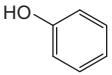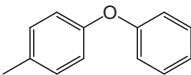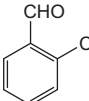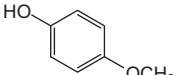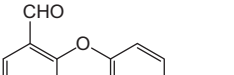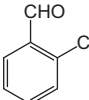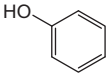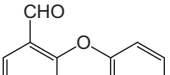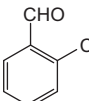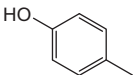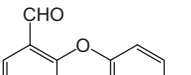
In conclusion, eco-friendly, heterogeneous reusable catalysts, Cu$_2$O/Cu-CNTs were prepared and successfully used for the C–O cross-coupling reaction to obtain various substituted diarylether derivatives with good to excellent yields under ligand-free conditions. The reaction was very sensitive to the steric effects of phenol. The catalyst was recovered by simple filtration without any further treatment and reused for several cycles with consistent activities.

Table 2
Coupling reaction of phenols with aryl halides (X = Cl, Br, I) in the presence of Cu$_2$O/Cu-CNTs catalyst[a]
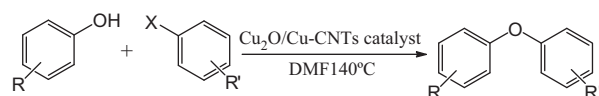
Entry	Aryl halides	Phenols	Product	Yield[b] (%)
1				96
2				97
3				65
4				46
5				68
6				25
7				52
8				83
9				67
10				95
11				94
12				77
13				67

Table 2 (continued)

Entry	Aryl halides	Phenols	Product	Yield[b] (%)
14	Iodobenzene	2-(t-Bu)phenol	2-(t-Bu)-diphenyl ether	42
15	Chlorobenzene	Phenol	Diphenyl ether	32
16	Chlorobenzene	4-methoxyphenol	4-methoxydiphenyl ether	62
17	4-chlorotoluene	Phenol	4-methyldiphenyl ether	45
18	2-chlorobenzaldehyde (CHO)	4-methoxyphenol	product	56
19	2-chlorobenzaldehyde (CHO)	Phenol	product	50
20	2-chlorobenzaldehyde (CHO)	4-methylphenol	product	55

[a] Reaction conditions: phenols (1.0 mmol), aryl halides (1.2 mmol), Cs_2CO_3 (1.0 mmol), Cu_2O/Cu-CNTs catalyst (0.06 g), DMF (5 mL), 140 °C, 24 h, under nitrogen atmosphere.

[b] Isolated yields.

Table 3
Recyclability studies of Cu_2O/Cu-CNTs catalyst for the Ullmann diaryl etherification[a]

Cycle	Yield[b] (%)
Native	94
1	95
2	92
3	93

[a] Reaction conditions: phenol (1.0 mmol), iodobenzene (1.2 mmol), Cs_2CO_3 (1.0 mmol), Cu_2O/Cu-CNTs catalyst (0.06 g), DMF (5 mL), 140 °C, 24 h, under nitrogen atmosphere.

[b] Isolated yields.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.079.

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