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Nano-CuO-Catalyzed Ullmann Coupling of Phenols with Aryl Halides under Ligand-Free Conditions

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Keywords: Nanostructures / Copper / Ligand-free conditions / Heterogeneous catalysis / Arylation / Catalyst recycling

Nano copper oxide has been found to be a highly efficient and reusable catalyst for the C–O cross-coupling of phenols with aryl halides under ligand-free conditions. With DMSO as solvent, Cs_2CO_3 and KOH are suitable bases for the cross-coupling reactions with phenyl iodides and bromides, respectively. Diaryl ethers with different substituted groups can be synthesized in moderate-to-good yields. The catalyst can be recycled at least five times without obvious loss in catalytic activity.

Introduction

Diaryl ethers are important structural motifs in numerous natural biologically active compounds, for example, K13, perrottetin and vancomycin,[1] as well as in many polymers such as poly(aryl ethers) (Figure 1). Copper-catalyzed Ullmann coupling of aryl halides with phenols represents the most popular choice for the synthesis of diaryl ethers on laboratory and industrial scales.[2] However, the utility of classical Ullmann coupling has been greatly limited by its harsh reaction conditions, for example, high temperatures (ca. 200 °C), the stoichiometric use of copper compounds and the low conversion of unactivated aryl halides.[3] Much effort has been devoted to developing more convenient methods of Ullmann-type *O*-arylation, mainly focusing on ligands,[4] bases,[5] copper species,[6] alternatives to aryl halides[7] and new experimental techniques.[6b,8] However, almost all of these methods involve ligands or well-defined catalysts/reagents, which may increase the cost and limit the scope of applications. Therefore, mild, simple and low-cost methods are still highly desirable.

On the other hand, nanomaterials with high surface areas as well as reactive morphologies have been widely studied. Very recently, the employment of nanocrystalline metal oxides as catalysts in organic synthesis has attracted much attention.[9,10] Nanomaterial-catalyzed reactions are generally characterized by easy product purification, efficient recycling of the catalyst and minimization of metal traces in the products. Herein we report a nano-CuO-catalyzed Ullmann cross-coupling of phenols with aryl halides under ligand-free conditions.

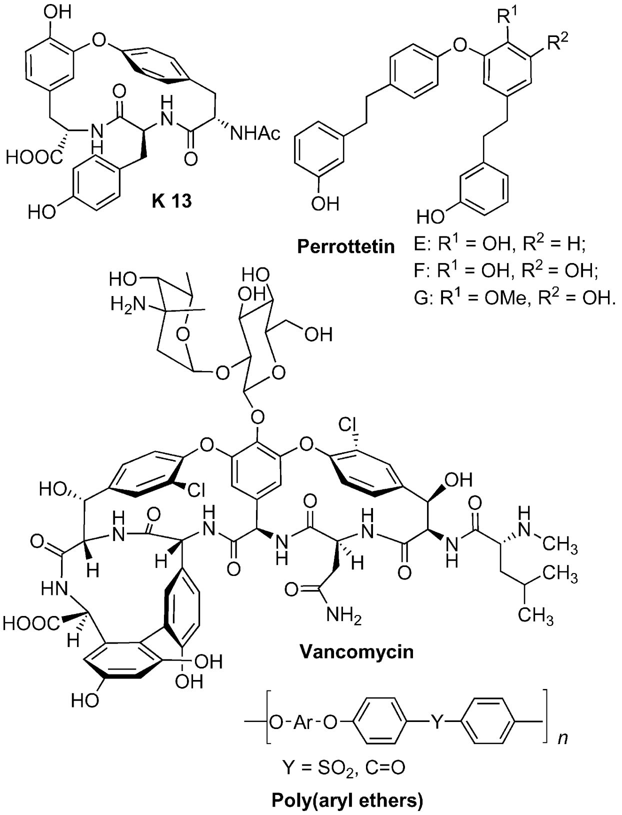

Figure 1. Examples of the diaryl ether structure in natural products and synthetic polymers.

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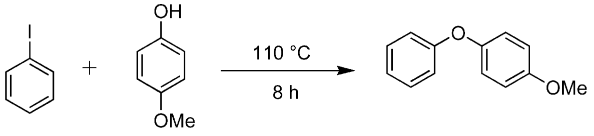
Results and Discussion

Initially, the coupling of 4-methoxyphenol with iodobenzene was chosen as a model reaction to study the effect of different copper species, bases, solvents, ratios of reactants, concentrations and temperature. A mixture of 4-methoxyphenol (1.0 mmol), iodobenzene (1.1 mmol) and 10 mol-% of catalyst were heated in the presence of base (Cs_2CO_3, 1.5 mmol) in DMSO (1 mL) at 110 °C under nitrogen. For the sake of experimental efficiency, most reactions were quenched after 8 h. First of all, catalysts of different copper salts were tested in this model reaction. Commercially available copper sources catalyze this reaction to afford the corresponding product in low yields of 22–28% (Table 1, Entries 1–3). No product was detected in the absence of copper as a catalyst (Table 1, Entry 4). Inspired by the fact that copper oxide also catalyzed the reaction, we prepared nanocrystalline copper oxide by a procedure similar to that described previously.[11] The nanoparticles were characterized by XRD and HRTEM analyses, and the average size of the copper oxide particles was about 28.5 nm (Figure 2).

Table 1. Coupling of 4-methoxyphenol with iodobenzene under different conditions.



Entry	Copper sources	Base	Solvent	Method[a]	Yield (%)[b]
1	$Cu(OAc)_2$	Cs_2CO_3	DMSO	A	22
2	$CuSO_4$	Cs_2CO_3	DMSO	A	28
3	CuO powder	Cs_2CO_3	DMSO	A	24, (46)[c]
4	none	Cs_2CO_3	DMSO	B	n.d.[d]
5	nano CuO	Cs_2CO_3	DMSO	A	44, (n.d.)[e]
6	nano CuO	Cs_2CO_3	DMF	A	21
7	nano CuO	KOH	DMSO	A	43
8	nano CuO	K_2CO_3	DMSO	A	41
9	nano CuO	K_3PO_4	DMSO	A	25
10	nano CuO	Cs_2CO_3	DMSO	C	62, (83)[f]
11	nano CuO	Cs_2CO_3	DMSO	C	12[g]

[a] Method A: ratio of phenol (1 mmol in 1 M solution)/iodobenzene/base/nano-CuO = 1.0:1.1:1.5:0.1. Method B: ratio of phenol (1 mmol in 1 M solution)/iodobenzene/base/nano-CuO = 1.0:1.1:1.5:0. Method C: ratio of phenol (1 mmol in 1 M solution)/iodobenzene/base/nano-CuO = 1.0:1.5:2.0:0.1. [b] Isolated yield. [c] The reaction was carried out according to Method C for 24 h. [d] n.d. = not detected. [e] In air. [f] The reaction time was lengthened to 18 h. [g] The reaction mixture was stirred at 90 °C for 23 h.

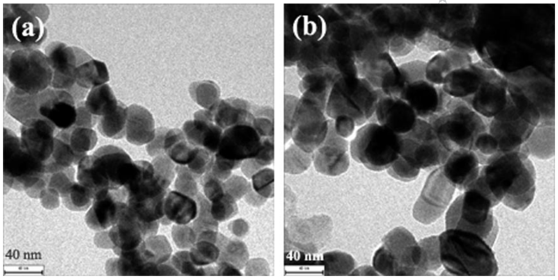


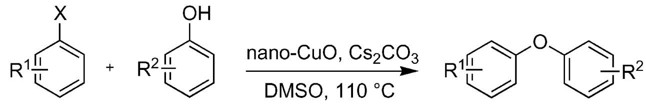
Figure 2. HRTEM images of (a) fresh nano-CuO particles and (b) nano-CuO particles after the fifth catalytic cycle.

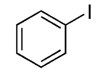
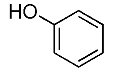
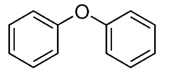
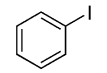
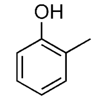
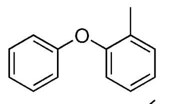
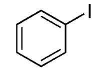
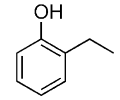
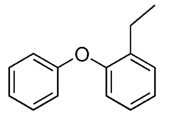
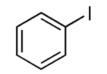
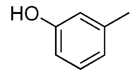
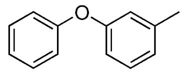
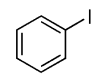
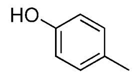
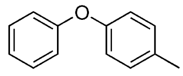
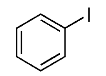
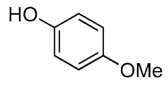
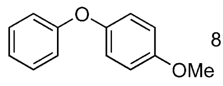
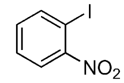
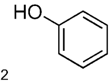
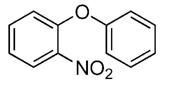
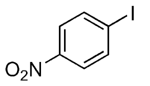
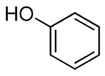
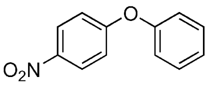
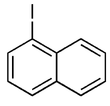
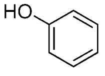
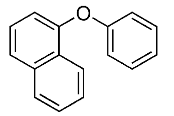
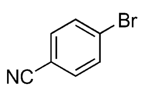
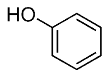
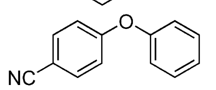
The reaction yield was dramatically increased to 44% when nanoparticles of copper oxide were used as the catalyst (Table 1, Entry 5). The high catalytic efficiency of nano copper oxide has also been reported by Punniyamurthy and co-workers in the construction of C–S and C–N bonds,[10a,10c] and Kantam et al. in the efficient arylation of heterocycles with activated chloro- and fluoroarenes.[10b] This encouraged us to optimize the reaction conditions further (Table 1). The catalyst loading and the concentration were also investigated in the model reaction (see the Supporting Information) and a 10 mol-% of loading was found to be the best choice. Common solvents, such as DMSO, DMF, dioxane, toluene and NMP, were tested (see the Supporting Information): DMSO gave the highest yield. Following these results, different bases, such as KOH, K_2CO_3 and K_3PO_4, were screened. The results indicated that Cs_2CO_3 can be replaced by K_2CO_3 or KOH (Table 1, Entries 7 and 8), but when K_2CO_3 or KOH was used, diphenyl ether was observed as a byproduct as a result of the competitive arylation of water with iodobenzene.[12] When the amount of base (Cs_2CO_3) was increased from 1.5 to 2.0 mmol and the amount of iodobenzene increased to 1.5 equiv., the yield was enhanced to 62% (Table 1, Entry 10). Temperature also had a large effect on the reaction. Below 100 °C the reaction produced the desired products in low yields (Table 1, Entry 11), but when the reaction was performed above 110 °C, there was no obvious improvement in yield.

After a systematic investigation, we identified the optimum conditions: nano-CuO as catalyst (10 mol-%), Cs_2CO_3 as base (2.0 equiv.) and DMSO as solvent at 110 °C with nitrogen protection (Table 1, Entry 10). Also, the isolated yield was increased to 83% when the reaction time was increased to 18 h under these conditions (Table 1, Entry 10).

With these optimized reaction conditions in hand, we employed a variety of substrates in an attempt to synthesize different diaryl ethers, as shown in Table 2. The experimental results indicated that substituents on the phenol ring or on the phenyl ring of the phenyl halides influenced the reaction greatly. For example, substitution of a methyl group at the *ortho* position of phenol incurs a reduction in yield from 84 to 73% (Table 2, Entries 1 and 2). With an increase in the substituent bulk from methyl to ethyl, the corresponding reaction yield decreased further to 54% (Table 2, Entry 3). Moreover, no reaction occurred under these conditions when the *ortho* position of phenol was occupied by a *tert*-butyl group. Although a *para*-methyl group showed a small positive effect (Table 2, Entry 5), a *tert*-butyl group hindered the reaction completely under these conditions, even when it was at the *para* position. This indicated that steric hindrance of the substituent on the phenol disfavours this reaction. As for electronic effects, electron-donating groups on the phenol ring had little effect on the reaction (Table 2, Entry 6). In contrast, electron-withdrawing groups on the phenol ring affected the reaction remarkably: no reaction occurred with a chloro substituent at the *para* position. As expected, an electron-withdrawing substituent on the phenyl ring of the phenyl halide favours this coupling (Table 2, Entries 7 and 8), whereas *para*-methoxy substitution led to the failure of the reaction. When iodobenzene was replaced by iodonaphthalene, the corresponding coupling reaction proceeded smoothly to give the aryl ether product in good yield (Table 2, Entry 9).

Table 2. Coupling of 4-methoxyphenol and iodobenzene with Cs_2CO_3.[a]

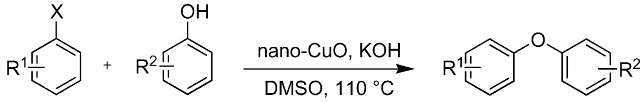


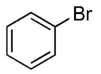
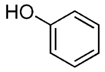
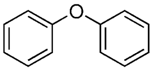
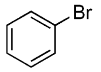
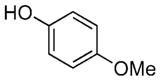
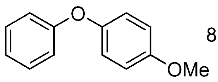
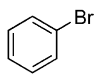
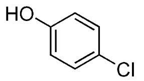
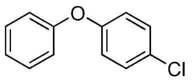
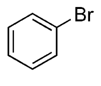
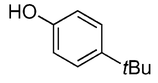
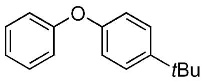
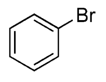
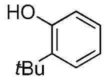
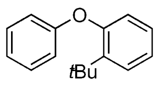
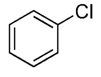
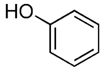
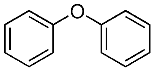
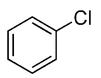
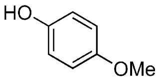
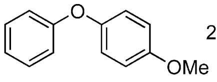
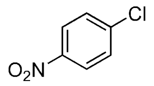
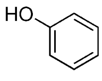
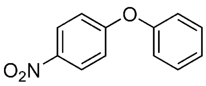
Entry	Aryl halides	Phenols	Products	Yields[b]
1				84
2				73
3				54
4				56
5				86
6				83
7				88
8				94
9				70
10				80

[a] Method C, 18–20 h. [b] Isolated yield.

To further extend the scope of the reaction, phenyl bromides were examined (Table 2, Entry 10, and Table 3 Entries 1–5). Generally, the reactivity of phenyl bromides is inferior to that of phenyl iodides. When an electron-withdrawing group such as a cyano group was installed on the phenyl ring of phenyl bromide, the corresponding coupling reaction proceeded smoothly to afford the coupling product in good yield under the same conditions as those used with the phenyl iodides (Table 2, Entry 10). However, other phenyl bromides did not react under the same conditions. Interestingly, when Cs_2CO_3 was replaced with KOH, phenyl bromides could be employed as the reaction substrates.[13] The corresponding coupling reactions were carried out to afford the coupling products in good yields (Table 3, Entries 1–5). Phenols with a bulky *tert*-butyl group or a bromo substituent, which were difficult substrates when Cs_2CO_3 was used as the base, can also be used in the presence of KOH to produce the coupling products in moderate yields (Table 3, Entries 3–5). Moreover, even phenyl chloride showed some reactivity when KOH was employed as the base, and the corresponding aryl ether products were ob-

Table 3. Coupling of phenols with bromobenzenes and chlorobenzenes.[a]



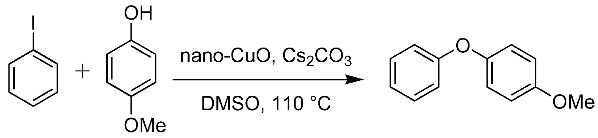
Entry	Aryl halides	Phenols	Products	Yields[b]
1				88
2				86
3				77
4				63
5				59
6				17
7				22
8				87

[a] Reaction conditions: nano-CuO (0.05 mmol), aryl halide (0.75 mmol), phenol (0.5 mmol), KOH (1 mmol), DMSO (0.5 mL), 110 °C, 18–20 h. [b] Isolated yield.

served (Table 3, Entries 6 and 7). In particular, a strongly electron-withdrawing substituent at the *para* position of phenyl chloride can increase the reaction yield efficiently (Table 3, Entry 8). The ligand-free system employing much cheaper phenyl bromides or phenyl chlorides and KOH is attractive and may find applications in the future.

As nano-CuO is a heterogeneous catalyst, the recyclability of the catalyst in this coupling reaction was examined. The coupling of 4-methoxyphenol with iodobenzene was chosen as a model reaction. After each cycle, the catalyst was recovered by simple centrifugation, washing with deionized water and ethanol and then drying in vacuo. The recovered nano-CuO was used directly in the next cycle. The recycling results are listed in Table 4 and show that the catalyst was still highly efficient after the fifth cycle. TEM images showed that the shape and size of the copper oxide nanoparticles has undergone almost no change even after the fifth cycle.

Table 4. Recycling of nano-CuO.[a]



Run	1	2	3	4	5
Time (h)	18	20	24	24	24
Yields (%)[b]	83	82	82	80	78

[a] Method C, 18–24 h. [b] Isolated yield.

Conclusions

We have prepared air-stable nano-CuO and employed it as an efficient catalyst in the Ullmann coupling reaction of phenols with aryl halides. The reaction can be carried out under mild conditions without any organic ligands or other auxiliaries, affording the corresponding aryl ethers in moderate-to-good yields. Cs_2CO_3 enabled the Ullmann-type *O*-arylation of phenyl iodides to be performed cleanly, whereas KOH activated this *O*-arylation when phenyl bromides or chlorides were employed as the reaction substrates. Moreover, the catalyst can be reused at least five times without obvious loss in catalytic activity. To the best of our knowledge this is the first example of a nano copper oxide as an efficient catalyst for C–O coupling under ligand-free conditions. The employment of nanoparticles as heterogeneous catalysts in other reactions is currently under study in our laboratory.

Experimental Section

General: All reactions were performed under pure and dry nitrogen in oven-dried glassware. DMSO was distilled from CaH_2 under nitrogen and stored over activated molecular sieves (4 Å). Cs_2CO_3 was ground to a fine powder before use. Cs_2CO_3 and all aryl halides and phenols were purchased from Sinopharm Chemical Reagent Co., Ltd., except for 2-ethylphenol, 2-*tert*-butylphenol and 4-bromobenzonitrile which were obtained from Alfa Aesar. Solid substrates were purified by recrystallization, and liquid substrates were purified by distillation under vacuum.

Preparation of CuO Nanoparticles: $Cu(NO_3)_2\cdot 3H_2O$ (3.624 g, 15 mmol) was dissolved in distilled water (50 mL) in air with stirring, and then the pH value of the solution was rapidly adjusted to 10 with Na_2CO_3 solution (1 M). The resultant solution was then aged together with the mother liquor at room temperature for 12 h. The final product was collected by filtration, washed with deionized water, dried at 60 °C for 24 h and then calcined at 350 °C for 24 h.

General Procedure for the Coupling of Phenols with Aryl Halides: A magnetic stirring bar, nano-CuO (4.0 mg, 0.05 mmol), Cs_2CO_3 (326 mg, 1 mmol) and phenol (0.5 mmol) were added into an oven-dried tube (5 mL) cooled under nitrogen. The tube was sealed with a septum, followed by three cycles of evacuation and back-filling with pure, dry nitrogen. Then DMSO (0.5 mL) and aryl halide (0.75 mmol) were injected through a syringe. The tube was sealed and heated to 110 °C under nitrogen and its content stirred at that temperature until the phenol was consumed, as determined by TLC. The reaction mixture was cooled to room temperature, diluted with water and extracted with ethyl acetate three times. The combined organic extracts were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Then the crude mixture was purified by column chromatography on silica gel to afford the product with high purity. The product was characterized by IR, ^1H and ^{13}C NMR spectroscopy and HR mass spectrometry.

Supporting Information (see footnote on the first page of this article): Experimental methods, details of optimization, characterization data and copies of spectra.

Acknowledgments

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