

Cu-nanoparticle catalyzed O-arylation of phenols with aryl halides via Ullmann coupling

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Abstract—Recyclable Cu-nanoparticles provide an efficient, economic, and novel method for the synthesis of diaryl ethers via Ullmann type coupling. This method provides a wide range of substrate applicability and avoids the use of a heavy metal co-catalyst and gives diaryl ethers in satisfactory yields.

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Diaryl ethers are an important class of organic compounds in the polymer and life science industries.¹ Many of them have been reported to have significant biological activity.^{2–6} Diaryl ethers are synthesized by the reaction of phenols and aryl halides.⁷

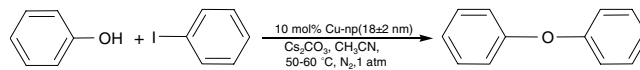
O-Arylation of phenols using aryl halides has been achieved using several methodologies. The important Ullmann protocol^{8–12} for the synthesis of diaryl ethers involves the reaction of an aryl halide with an alkali metal aryl oxide in the presence of copper salts. Other methods include Pummerer type rearrangements, inter- and intramolecular S_NAr reactions, arene metal complexes, thallium-promoted oxidative coupling, Pt-promoted coupling, phenolic addition to cyclohexene oxides, and Diels–Alder cyclization.

Several non-Ullmann methods^{11c} such as the Buchwald,^{13,14} Hartwig,^{15,16} Evans,¹⁷ and Chan¹⁸ coupling methods have been developed for this coupling. Further, microwave^{19–25} and ultrasonic²⁶ irradiation have been used in the presence of a Zn(I)/Cu(I) salt. However, these reagents, used in stoichiometric amounts,²⁷ are highly moisture sensitive, and require strictly controlled reaction conditions. These reactions were carried out

either in toxic solvents such as toluene or in the presence of expensive ionic liquids²⁸ with hazardous reagents at high temperature using high catalyst loadings (50 mol %) giving unsatisfactory yields. Metal nanoparticles are employed as heterogeneous catalysts and can be recycled, which is an advantage compared to other catalysts.

In continuation of our interest in exploring catalytic methodology²⁹ and the role of transition metal nanoparticles³⁰ in organic transformations, we report herein recyclable Cu-nanoparticles as the catalyst for an efficient synthesis of diaryl ethers. Initially, to examine the catalytic activity of Cu-nanoparticles, we studied the reaction of phenol (1 mmol) with iodobenzene (1 mmol) in the presence of 10 mol % of Cu-nanoparticles (Cu-np) and Cs₂CO₃ as base in acetonitrile (5 mL) at 50–60 °C under an N₂ atmosphere (Scheme 1).³¹

The diaryl ether was formed in 91% yield in 4 h. In the absence of catalyst, the ether was obtained in only 5% yield in 42 h (Table 1). Increasing the loading of Cu-nanoparticles to 50 mol % gave the diaryl ether in 95% yield in 1.5 h (Table 1, entry 5). Thus an increase in



Scheme 1. Cu-nanoparticle catalyzed reaction of iodobenzene with phenol.

Keywords: Cu-nanoparticles; Phenols; Aryl halides; Diaryl ethers; Recyclability.

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Table 1. Optimization of the concentration of Cu-nanoparticles for O-arylation^a

Entry	Cu-np (18 ± 2 nm) (mol %)	Time (h)	Yield ^b (%)
1	0	42	5
2	5	11	82
3	10	4	91
4	30	3	93
5	50	1.5	95

^a Reaction conditions: 1.0 equiv of aryl iodide, 1.0 equiv of phenol, 1.5 equiv of Cs₂CO₃, *x* mol % Cu-np (18 ± 2) nm; CH₃CN; 50–60 °C; N₂; 1 atm.

^b Isolated and unoptimized yields.

the concentration of catalyst not only promotes the reaction but also resulted in an increased yield (Table 1). However, at room temperature, lower yields were obtained even after long reaction times.

All further optimizations were carried out at 50–60 °C with 10 mol % of Cu-np. Cu-nanoparticles of different sizes, ranging from 10 nm to 70 nm in diameter, were prepared in an aqueous core of reverse micellar droplets.^{32–35} The average particle size was confirmed as 10–18 nm through quasi-elastic light scattering data (QELS) (Fig. 1a) and transmission electron microscopy (TEM) (Fig. 1b). Our study showed that the catalytic action of the nanoparticles was dependent on the nanoparticle size (Table 2).

The maximum reaction rate was observed for a particle of an average diameter of about 20 nm. With a decrease in particle size, the reaction rate decreased. For particles above 20 nm, there was also a steady decline in reaction rate. We suggest that in the case of the particles of average size less than 20 nm, a downward shift of the Fermi level takes place, with a consequent increase of band gap energy. As a result, the particles require more energy to pump electrons to the adsorbed ions for the electron transfer reaction. This leads to a reduction in reaction rate. On the other hand, for nanoparticles >20 nm in diameter, the change of Fermi level is not appreciable,

Table 2. Size screening of Cu-nanoparticles in the reaction of iodobenzene and phenol^a

Entry	Particle size(±2) (nm)	Time (h)	Yield ^b (%)
1	10	4	87
2	20	3	91
3	30	3.5	85
4	50	6	73
5	70	9	67

^a Reaction conditions: 1.0 equiv of aryl iodide, 1.0 equiv of phenol, 1.5 equiv of Cs₂CO₃, 10 mol % Cu-np (*x* ± 2) nm; CH₃CN; 50–60 °C; N₂; 1 atm.

^b Isolated and unoptimized yields.

however, these particles exhibit less surface area for adsorption, so a decrease in catalytic efficiency results.

It is important to stress that the catalyst was recycled and reused for four to five runs. Further, starting material was added to the reaction mixture and the reaction allowed to proceed for an additional 6 h, resulting in an 87% yield (Table 3, run 1).

Conglomeration of Cu-nanoparticles causes a change in size. Cu-nanoparticles were separated from the reaction mixture by mild centrifugation at 2000–3000 rpm at 10 °C for 5 min. QELS data (Fig. 2) clearly showed that conglomeration of the Cu-nanoparticles had occurred.

The basicity of the base plays an important role in the reaction of phenols and aryl halides. The Cu-nanoparticle catalyzed reaction is much faster with Cs₂CO₃ than with K₂CO₃ or Na₂CO₃ due to the enhanced basicity of Cs₂CO₃.

Table 3. Recycling yields

No. of cycles ^a	Fresh	Run 1	Run 2	Run 3	Run 4
Yield ^b (%)	91	87	81	72	63
Time (h)	4	6	9	11	12

^a Reaction conditions: 1.0 equiv of aryl iodide, 1.0 equiv of phenol, 1.5 equiv of Cs₂CO₃, 10 mol % Cu-np (*x* ± 2) nm; CH₃CN; 50–60 °C; N₂; 1 atm.

^b Isolated and unoptimized yields.

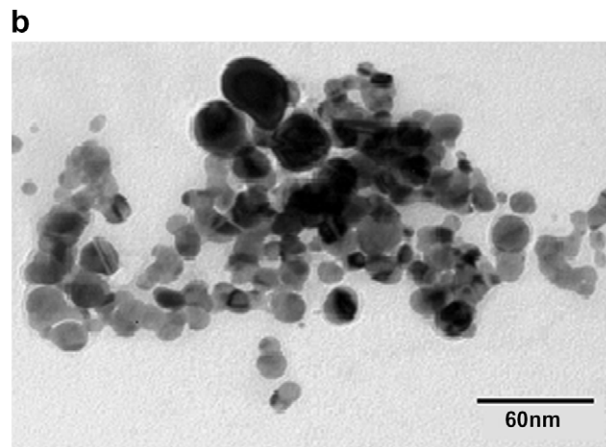
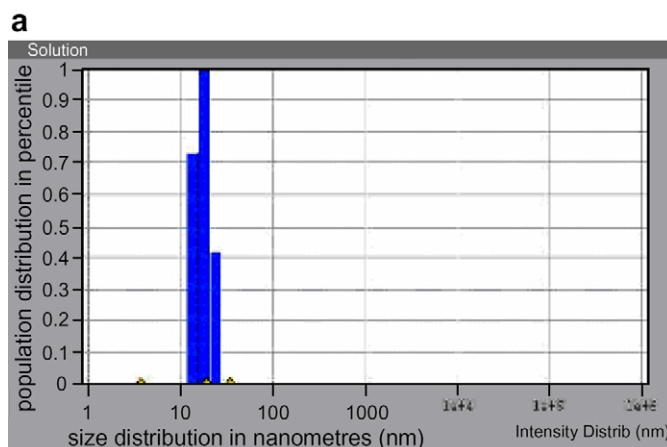


Figure 1. (a) QELS data of Cu-nanoparticles: plot of population distribution in percentile versus size distribution in nanometers (nm); (b) TEM image of Cu-nanoparticles.

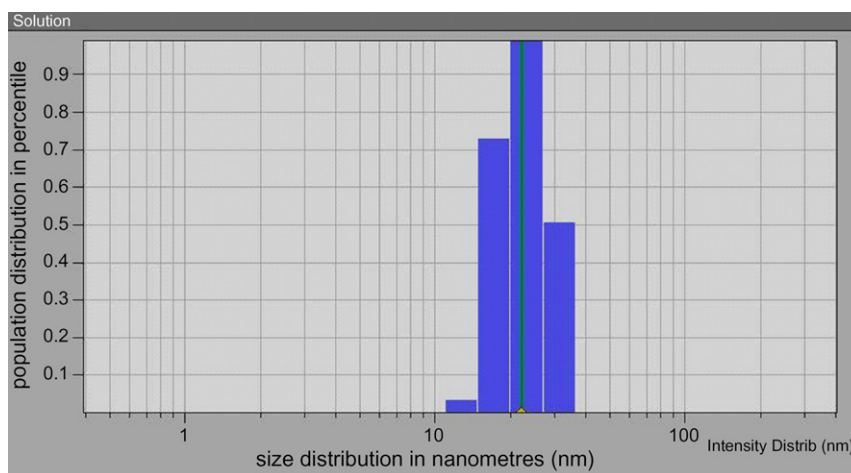
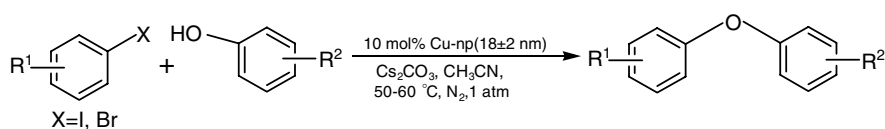


Figure 2. QELS data of recycled Cu-nanoparticles: plot of population distribution in percentile versus size distribution in nanometres (nm).

Table 4. Reaction of aryl halides with substituted phenols using Cu-nanoparticles as catalyst^a



Entry	Aryl halide	Phenol	Time (h)	Product	Yield ^b (%)
1			4		91
2			4		87
3			4		85
4			4		81
5			4		95
6			4		92
7			4		68
8			4		84
9			4		87
10			4		90

^a Reaction conditions: 1.0 equiv of aryl iodide, 1.0 equiv of phenol, 1.5 equiv of Cs₂CO₃, 10 mol % Cu-np (18 ± 2) nm; CH₃CN; 50–60 °C; N₂; 1 atm.

^b Isolated and unoptimized yields.

Finally, we examined the coupling reaction with various phenols and aryl halides possessing a wide range of

functional groups. Phenols possessing electron-donating groups (Table 4, entries 5 and 10) afforded better yields,

than those with electron-withdrawing groups (Table 4, entries 3 and 4).

In conclusion, a novel, easy, and economical method for the synthesis of diaryl ethers has been developed using Cu-np as a catalyst. The process is simple and allows the formation of a diverse range of diaryl ethers in excellent yields. Overall, this methodology offers competitive advantages such as recyclability of the catalyst without further purification or without using additives or cofactors, low catalyst loading, broad substrate applicability, and high yields in short reaction times.

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- In a 50 mL round bottom flask, the phenol (1 mmol), aryl halide (1 mmol), and Cs₂CO₃ (1.5 mmol) in CH₃CN (5 mL) were stirred under a nitrogen atmosphere and Cu-nanoparticles (10 mol % 18 ± 2 nm) were added. The reaction mixture was allowed to stir at 50–55 °C for the appropriate time (Table 4). The extent of reaction was monitored by TLC. After completion of the reaction, the resulting mixture was centrifuged at 2000–3000 rpm, at 10 °C for 5 min. The organic layer was decanted and the remaining Cu-nanoparticles were reused for further

reactions. The organic layer was washed with brine (15 mL) and the aqueous extracted with diethyl ether (15 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (60–120 mesh size) using 25% ethyl acetate in petroleum ether as eluent to afford the desired product. The structures of all the products were unambiguously established on the basis of their spectral analysis (IR, ^1H , ^{13}C NMR, and GC–MS mass spectral data). All the products are known compounds.

32. A chemical method involving the reduction of Cu^{2+} ions to $\text{Cu}(0)$ in a reverse micellar system was employed to prepare the Cu-nanoparticles (Cu-np). Pol(oxyethylene) (tetramethyl)-phenyl ether, commercially known as Tritonx-100 (TX-100) was used as surfactant in the process. To a reverse micellar solution of aq CuSO_4 , reverse micellar solution of aq N_2H_2 was added with constant

stirring. The resulting solution was allowed to stir for 3 h under N_2 to allow complete Oswald ripening (particle growth). The Cu-np was extracted using absolute ethanol followed by centrifugation. By varying the water content parameter, W_0 (defined as the molar ratio of water to surfactant concentration, $W_0 = [\text{H}_2\text{O}]/[\text{surfactant}]$) the size of the nanoparticles could be controlled. The nanoparticles prepared were round in shape, with an average size of 10–18 nm as confirmed by TEM and QELS data. The metallic nature of the $\text{Cu}(0)$ nanoparticles was confirmed by a characteristic UV absorption of the particles dispersed in cyclohexane (580 nm).

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