Cul-Nanoparticles-Catalyzed Selective Synthesis of Phenols, Anilines, and Thiophenols from Aryl Halides in Aqueous Solution

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S Supporting Information

ABSTRACT: CuI-nanoparticles-catalyzed selective synthesis of phenols, anilines, and thiophenols from aryl halides was developed in the absence of both ligands and organic solvents. Anilines were formed selectively with ammonia competing with hydroxylation and thiophenols were generated selectively with sulfur powder after subsequent reduction competing with hydroxylation and amination.



Phenols, anilines, and thiophenols are important building blocks for constructing natural products, pharmaceutical and medicinal compounds, as well as in polymers and materials.¹⁻³ The development of a mild and highly efficient method for synthesis of them over classical protocols has gained considerable attention in synthetic chemistry. Recently, several efficient palladium/phosphine-catalyzed processes have been developed for selective formation of phenols,⁴ anilines,⁵ and thiophenols.⁶ However, the replacement of palladium with less expensive copper(I) salt as catalyst would be allowed for economic benefits and low toxicity issues. The development of a cheaper system enabling the hydroxylation,⁷ amination,⁸ and thiolation⁹ of aryl halides has become an important goal. More recently, a highly efficient copper-catalyzed procedure for the direct hydroxylation of aryl halides in the presence of ligands was disclosed by You^{/c} and Taillefer^{7c} independently and research showed that a welldefined ratio of water/organic solvent was the key factor, whereas water alone was inefficient. It is well-known that water is the most economical and environmentally friendly solvent in the world.¹⁰ Organic solvents contributed the largest amount of "auxiliary waste" in most chemical productions.¹¹ Very recently, efficient copper-mediated and ligand-assisted catalytic systems for direct conversion of aryl halides into phenols^{7f,g} or anilines^{8a,b} in water have been developed. Ma developed a protocol for thiophenols involving CuI-catalyzed coupling of aryl iodides with sulfur and subsequent reduction.⁹ Unfortunately, all the above catalytic reactions are inefficient in neat aqueous medium in the absence of ligands.

Metal nanoparticles have drawn much attention due to the advantages offered by these "semi-heterogeneous catalysts". The

characteristics of heterogeneous catalysis (recovery and recyclability) and those of homogeneous catalysis (relatively low catalyst loadings and good selectivity) were combined in nanoparticles catalyst. In addition, because of their large surface area, metal nanoparticles usually showed high reactivity under mild conditions.¹² Thus, transition metal nanoparticles have been used widely as catalysts for organic synthesis.¹³ Herein, we disclosed a very simple, efficient, ligand-free CuI-nanoparticlescatalyzed selective synthesis of phenols with water as the solvent under very mild conditions.¹⁴ To our surprise, the coupling reaction gave selectively anilines when NH₃·H₂O was added into the system. And thiophenols would be obtained selectively after reduction appending sulfur powder. To the best of our knowledge, there are no reports on this interesting chemoselective arylation.

The study was initiated by an investigation of hydroxylation of iodobenzene with CuI nanoparticles in water without any ligands. As shown in Table 1, tetra-*n*-butylammonium hydroxide was used as the base at 60 °C with CuI nanoparticles as the catalyst (1.5 mol %) in water (Table 1, entry 1), and the reaction gave selectively phenol in 97% yield, the corresponding symmetric ether appearing in only 0.3% yield. When the base was altered to KOH, CsOH, Me₄NOH, and Et₄NOH, low yields were obtained (Table 1, entries 2–5). The copper(I) salts such as CuBr, CuCl, Cu₂O, and CuI were found to be inferior to CuI nanoparticles (Table 1, entries 6–9). Control experiments confirmed that no conversion occurred without catalyst (Table 1,

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 Table 1. Optimization of Hydroxylation of Aryl Halides

 Catalyzed by CuI Nanoparticles in Water^a



entry	Х	[Cu] (mol %)	base	T/°C	yield/% ^b
1	Ι	CuI(np(1.5))	<i>n</i> Bu ₄ NOH	60	97
2	Ι	CuI(np(1.5))	КОН	60	57
3	Ι	CuI(np(1.5))	CsOH	60	63
4	Ι	CuI(np(1.5))	Me ₄ NOH	60	79
5	Ι	CuI(np(1.5))	Et ₄ NOH	60	87
6	Ι	CuBr(10)	nBu ₄ NOH	60	19
7	Ι	CuCl(10)	nBu ₄ NOH	60	16
8	Ι	$Cu_2O(10)$	nBu ₄ NOH	60	15
9	Ι	CuI(10)	<i>n</i> Bu ₄ NOH	60	33
10	Ι		<i>n</i> Bu ₄ NOH	60	trace
11	Ι	CuI(np(1.5))	<i>n</i> Bu ₄ NOH	50	80
12	Ι	CuI(np(1.0))	<i>n</i> Bu ₄ NOH	60	71
13	Ι	CuI(np(1.0))	<i>n</i> Bu ₄ NOH	80	83
14^c	Ι	CuI(np(1.5))	nBu ₄ NOH	60	75
15^d	Br	CuI(np(10))	nBu ₄ NOH	60	trace
16^d	Br	CuI(np(10))	nBu ₄ NOH	80	11
17^d	Br	CuI(np(50))	nBu ₄ NOH	80	42
$18^{d,e}$	Br	CuI(np(50))	<i>n</i> Bu ₄ NOH	80	45
19^d	Br	CuI(np(50))	<i>n</i> Bu ₄ NOH	90	27
20^d	Br	CuI(np(110))	<i>n</i> Bu ₄ NOH	80	78
$21^{d,e}$	Cl	CuI(np(110))	<i>n</i> Bu ₄ NOH	80	12

^{*a*} Reaction conditions: halogenated benzene (1.0 mmol), base (3.0 equiv), H_2O (2.0 mL) under N_2 for 24 h. ^{*b*} Determined by GC. ^{*c*} Reaction time is 15 h. ^{*d*} Reaction time is 48 h. ^{*e*} With 5.0 equiv of nBu_4NOH . np = nanoparticles.

entry 10). Low yields were obtained when the reaction time, temperature, or amount of CuI nanoparticles were reduced (Table 1, entries 11-14). The optimal conditions of 1.5 mol % of CuI nanoparticles, 3.0 equiv of *n*Bu₄NOH in water at 60 °C were used for further investigations.

With this efficient system in hand we next extended the scope of the substrate to various aryl iodide derivatives (Table 2). We found that the reaction was applicable to a broad range of derivatives and was not affected strongly by electron-donating or electron-withdrawing groups. But, the reactions seemed to be sensitive to the steric hindrance on the substrate. For example, 1-chloro-2-iodobenzene was hydroxylated under optimized conditions, only 47% isolated yield was obtained. Fortunately, the reaction was accelerated significantly at elevated temperature and longer reaction time. Almost quantitative conversions were obtained from 4-iodobenzoic acid and 2-iodobenzoic acid to the corresponding products.

Although aryl bromides are less reactive than aryl iodides, the greater interest for industrial applications fixed our attention. In spite of the slightly higher temperature that was needed, a series of phenols were generated from activated aryl bromides (Table 3). We only obtained a few phenols whose yields are very close to the catalyst loading (Table 1, entries 16–20) with bromobenzene as substrate. The yield decreased with reaction

Table 2. Hydroxylation of Aryl Iodides Catalyzed by CuI Nanoparticles in Water^a



^{*a*} CuI nanoparticles (1.5 mol %), Ar–I (1.0 mmol), 40% nBu_4 NOH aq (2.0 mL/3.0 equiv) at 60 °C under N₂ for 24 h; isolated yield. ^{*b*} At 80 °C for 36 h.

 Table 3. Hydroxylation of Aryl Bromides Catalyzed by CuI

 Nanoparticles in Water^a



^{*a*} CuI nanoparticles (1.5 mol %), Ar-Br (1.0 mmol), 40% *n*Bu₄NOH aq (2.0 mL/3.0 equiv) at 80 °C under N₂ for 48 h; isolated yield. ^{*b*} With 110 mol % of CuI nanoparticles, *n*Bu₄NOH 40% aq (3.3 mL/5.0 equiv).

temperature elevating, probably because nBu_4NOH decomposed at higher temperature (Table 1, entry 19). However, we were able to obtain phenol in good yield (78%) when the amount of catalyst was increased to 110 mol % (Table 1, entry 20). This method was extended successfully to aryl bromides with electron-donating substituents such as *p*- or *o*-methyl and *p*-, or *o*-methoxy. 1- and 2-bromonaphthalenes were also converted selectively into the corresponding naphthols under these conditions.

Inspired by metal-catalyzed chemoselective *N*- or *O*-arylations,¹⁵ we wondered whether *N*-arylation would take place when aqueous NH_3 solution was added into the system with existing N, O nucleophilic competition. To our delight, the *N*-arylation readily occurred even at room temperature, and the product of *O*-arylation was detected in small quantity (<3%).

Next, the scope of aryl iodides was investigated for the *N*arylation reaction with aqueous ammonia at room temperature in Table 4. CuI-Nanoparticles-Catalyzed Amination of Aryl Iodides with $NH_3 \cdot H_2O$ at Room Temperature in Water^{*a*}



^{*a*} CuI nanoparticles (1.5 mol %), Ar–I (1.0 mmol), 40% *n*Bu₄NOH aq (1.3 mL/2.0 equiv), commercial 28% aqueous NH₃ (5.0 equiv) at room temperature (25 °C) under N₂ for 24 h; isolated yield. ^{*b*} Reaction time is 48 h. ^{*c*} At 45 °C. ^{*d*} 4,4'-Diiodobiphenyl as substrate, commercial 28% aqueous NH₃ (10.0 equiv).

 Table 5. CuI-Nanoparticles-Catalyzed Amination of Aryl

 Bromides^a



^{*a*} CuI nanoparticles (3.0 mol %), Ar—Br (1.0 mmol), 40% nBu_4NOH aq (1.3 mL/2.0 equiv), commercial 28% aqueous NH₃ (10.0 equiv) at 80 °C under N₂ for 48 h; isolated yield.

water (Table 4). In general, all the aryl iodides gave the corresponding anilines with good to excellent yields. Ortho substituents had no obvious effect on yields of products to some extent, and a variety of functional groups could be tolerated in the reaction.

Although little *p*-nitroaniline was detected when *p*-nitrobromobenzene was reacted with aqueous ammonia at room temperature, 73% yield was obtained when the reaction was carried out at 80 °C for 48 h. Futhermore, *p*-nitroaniline was obtained with 87% yield when 3.0 mol % of CuI nanoparticles and 10.0 equiv of NH₃ were applied. As shown in Table 5, all the examined aryl and heteroaryl bromides coupled with aqueous ammonia to afford the corresponding anilines with good to excellent yields. On the other hand, aryl bromides bearing electron-donating substituents were less effective. In addition, the reactivity of aryl chlorides decreased dramatically in the present system.¹⁶





^{*a*} CuI nanoparticles (1.5 mol %), Ar-X (1.0 mmol), 40% *n*Bu₄NOH aq (1.3 mL/2.0 equiv), sulfur power (3.0 equiv) at 40 °C under N₂ for 24 h; isolated yield. ^{*b*} At room temperature (25 °C). ^{*c*} With 3.0 mol % CuI nanoparticles at 80 °C for 48 h.









We were pleased to observe that the coupling reaction produces selectively thiophenols after subsequent reduction when sulfur powder was added instead of aqueous ammonia (Table 6).¹⁷ Aryl thiols were obtained with both inactivated and activated aryl iodide derivatives. No matter if the aryl iodides were electron-rich, electron-poor, or sterically hindered, all of them afforded good to excellent yields. Moreover, aryl thiols of high yield were obtained with aryl bromides bearing electronwithdrawing groups. Low conversions occurred for inactivated aryl bromides.

Since chemoselective *N*-arylation and *S*-arylation were accomplished as opposed to *O*-arylation, a competitive experiment was performed to check out which arylation reaction would occur when the three substrates existed at the same time (Scheme 1). Under the standard conditions (see SI), iodobenzene was reacted in the presence of both $NH_3 \cdot H_2O$ and *S*, thiophenol





run	catalyst recovery (%)	product yield (%) ^c
1^a	95	95
2^{b}	89	87
3^b	82	80

 a CuI nanoparticles (1.5 mol %), iodobenzene (1.0 mmol), 40% $n{\rm Bu}_4{\rm NOH}$ aq (1.3 mL/2.0 equiv), commercial 28% aqueous NH_3 (5.0 equiv) at 25 °C under N_2 for 24 h. b The recovered catalyst was used under identical reaction conditions to those for the first run. c Determined by GC.



Figure 1. (a) TEM image of fresh CuI nanoparticles; (b) TEM image of CuI nanoparticles after the third catalytic cycle; (c) TEM image of fresh CuI nanoparticles at 50 nm; (d) XRD pattern of fresh CuI nanoparticles; (e) XRD pattern of CuI nanoparticles after the third catalytic cycle.

was formed selectively after reductive step, proving the order of S > N > O.

Aminophenols constitute a common structural motif in various potentially useful therapeutic agents and drug candidates.¹⁸ The similarity in conditions between *N*-arylation and *O*-arylation suggested that the present protocol could be used as a tandem reaction, and this was indeed the case (Scheme 2). The synthesis of 4-aminophenol was achieved by hydroxylation of the C–I bond of 1-bromo-4-iodobenzene, followed by amination of the C–Br bond on increasing the temperature and reaction time.

It was a heterogeneous process and the catalyst was recyclable with slight loss of activity (Table 7).¹⁹ After completion of amination of iodobenzene, the catalyst was recovered from the reaction mixture by centrifugation and reused for the fresh reaction and only a slight decrease in catalytic activity was observed. In addition, in the TEM analysis of CuI nanoparticles, interestingly, the shape and size of the nanoparticles remained unchanged before and after the reaction (Figure 1a-c). Likewise, the powder X-ray diffraction analysis exhibited identical peaks for both the fresh and recovered CuI nanoparticles (Figure 1d,e).

In conclusion, we have demonstrated that selective *O*-arylation,²⁰ *N*-arylation, and *S*-arylation could be achieved in water without assisted ligand at relatively mild conditions (no higher than 80 °C).^{4a} A variety of aryl iodides and bromides could be coupled with available nBu_4NOH , $NH_3 \cdot H_2O$, and *S* in this simple and efficient protocol to give the corresponding products in high yields. The competition experiment showed that S had the best reactivity. Furthermore, the catalyst could be reused for three cycles with slight loss of its activity.

EXPERIMENTAL SECTION

General Procedure for Hydroxylation of Aryl lodides. An oven-dried Schlenk tube equipped with a magnetic stirring bar was charged with CuI nanoparticles (1.5 mol %, 2.9 mg), the aryl iodides if a solid (1 mmol). The tube was evacuated and backfilled with nitrogen. Under a counter flow of nitrogen, aryl iodides if a liquid (1 mmol, 1 equiv) and degassed 40% tetra-*n*-butylammonium hydroxides water solution (2.0 mL) were added. The tube was sealed and the mixture was allowed to stir at 60 °C for 24 h. The reaction mixture was then allowed to cool to ambient temperature, then 10 mL of ethyl acetate and 1 mL of HCl (37%) were added. For the general workup and detailed experiments, please see the Supporting Information.

ASSOCIATED CONTENT

Supporting Information. Preparation of the catalyst, general synthetic procedures, and characterization of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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