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Heterogeneous copper-catalyzed hydroxylation of aryl iodides under air conditions†

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In this work, the ligand-free heterogeneous copper Cu-g-C_3N_4 was synthesized and used for the hydroxylation of aryl iodides to synthesize phenols using cheap bases. The catalyst was conveniently prepared, air-tolerant, reusable and scalable, and is very efficient for a wide range of substrates. The synthesis of substituted phenols can be carried out under air conditions and has great potential for practical applications.

Serving as the structural constituents of pharmaceuticals, materials, and natural compounds, phenols are very important synthetic intermediates with numerous applications in manufacturing of petrochemical, agrochemical polymers and other chemicals.[1] Effective synthesis methods for phenols are highly required.[2] Functionalized phenols can be synthesized through different routes, including coupling of hydroxide with aryl halides,[3] benzyne protocol,[4] C–H activation/hydroxylation[5] and transformation of arene diazonium salts mediated by copper.[6] Amongst these approaches the most attractive method is the conversion of aryl halides to phenols *via* the coupling with hydroxide using transition metal salts as the catalysts. Different types of catalysts have been developed, including homogeneous Pd/ligand catalyst systems,[3] semi-heterogeneous Pd/polyaniline catalysts,[7] homogeneous CuI/ligand catalyst systems,[8–10] and Fe/*N*,*N*′-dimethylethylenediamine catalysts.[11]

Buchwald and co-workers[3a] did the first work on the hydroxylation in 2006. They realized the preparation of phenols from aryl/heteroaryl bromides and chlorides by applying monodentate phosphine ligands with Pd_2dba_3 as the catalyst under an inert atmosphere. Subsequently, some efficient catalytic systems based on palladium/phosphine ligands have been developed by the groups of Willis,[3b] Kwong,[3c] Beller,[3d,e] and Stradiotto.[3f]

Using cheap metals instead of noble metals is always the pursuit of green catalysis. In 2009, the synthesis of phenols by direct cross-coupling of aryl iodides and hydroxide salts with CuI as the catalyst was reported simultaneously using either a 1,3-diketone[8] or a 1,10-phenanthroline[9] ligand in an aqueous DMSO system under a nitrogen atmosphere. More recently, several other ligands such as lithium pipecolinate,[12] 8-hydroxyquinoline-N-oxide,[13] D-glucose,[14] 8-hydroxyquinoline,[15] pyridine-2-aldoxime,[16] 8-hydroxyquinalidine[17] and glycolic acid[18] were developed. These results indicate that the transformation is highly dependent on the use of various special ligands.

Cu-based catalysts have been studied most extensively for this kind of reaction because they have some unique advantages. However, most reported studies were homogeneous, which need special ligands and it is very difficult to recycle the catalysts. A sulfonic acid resin (INDION-770) in combination with copper salts[19] and CuO supported on mesoporous silica[20] were reported but expensive CsOH is required. Tetra-*n*-butylammonium hydroxide was also employed as the base using CuI-nanoparticles as catalysts, the reactions were carried out under an inert atmosphere with a long reaction time.[21] Copper-MOF was also found to be active in the hydroxylation of aryl iodides, unfortunately, complete decomposition of MOFs occurred after the reaction and the catalyst cannot be recycled.[22] Obviously, developing heterogeneous, low cost, highly efficient, and recyclable catalysts for the reactions is highly desirable, but is challenging.

Mesoporous graphitic carbon nitride (mpg-C_3N_4) has recently found wide applications in catalysis due to its special structure and properties.[23] The mpg-C_3N_4 materials show great potential in fabricating supported catalysts.[24] In the present work, we synthesized a copper-doped graphitic carbon nitride catalyst (Cu-g-C_3N_4) by using cheap urea and $Cu(NO_3)_2$ as the precursors through a facile and efficient method. The catalyst was successfully applied in the synthesis of phenols from aryl iodides and hydroxide. Good to excellent yields of phenols could be obtained under air conditions with low Cu loading. The catalyst could be reused at least 5 times without a decrease in yield. More importantly, the Cu-g-C_3N_4 catalyzed hydroxylation of aryl iodides can be

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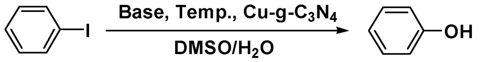
conducted on 10 g scales under experimental conditions, thus has great potential in application for synthesizing substituted phenols.

Initially, we selected iodobenzene as the model substrate to optimize the reaction conditions, and the results are summarized in Table 1. In DMSO aqueous solution with a DMSO and water volume ratio of 1 : 1, a yield of 98.6% was achieved at 120 °C when using cesium hydroxide (6.0 eq.) as the nucleophile and Cu-g-C_3N_4 (8 mol%) as catalyst (Table 1, entry 1). When KOH or NaOH was used as the nucleophile, almost quantitative product phenol was formed and no by-product was detected by GC-MS (Table 1, entries 2 and 3). Encouraged by these good results, the effects of concentrations of bases, reaction temperature and reaction solvents on the phenol synthesis were further investigated. It is worth noting that at lower concentrations of the bases or when the temperature was below 120 °C, the yield of phenol was low (Table 1, entries 4–12). Solvent composition has remarkable influence on the yield of the product (Table 1, entries 6 and 13–18). Only 14.6% yield of phenol was formed in pure DMSO (Table 1, entry 13), and no product was detected in pure water (Table 1, entry 18). To further optimize the reaction conditions, the effect of the amount of Cu-g-C_3N_4 catalyst on the reaction was studied. It can be known from Table 1 that reducing the amount of Cu from 8 mol% to 4 mol% did not reduce the yield, and the reaction could finish with excellent yields in 12 h (Table 1, entries 3, 19 and 20). However, when the amount of Cu-g-C_3N_4 catalyst was further decreased to 2 mol%, the yield of phenol was only 50.9% after 24 h (Table 1, entry 21). The above results indicate that 4 mol% Cu-g-C_3N_4 was the reasonable amount of the catalyst. An excellent result was obtained when the reaction was carried out with 4 mol% Cu-g-C_3N_4 using NaOH as the base in DMSO aqueous solution at 120 °C under air conditions (Table 1, entry 20). To verify the crucial role of the Cu-g-C_3N_4 catalyst for the reaction, a control experiment was also conducted in the absence of the Cu-g-C_3N_4 catalyst, and the reaction did not occur (Table 1, entry 22). To ascertain the role of air in the catalytic reaction, we conducted a control experiment under an Ar atmosphere. The result is also listed in Table 1. Under an Ar atmosphere, the reaction can also be carried out with excellent yield (Table 1, entry 23). The result indicated that air did not affect the catalytic reaction.

Table 1 Optimization of hydroxylation of iodobenzene catalyzed by Cu-g-C_3N_4 in DMSO aqueous solution[a]



Entry	Base/eq.	Temp./°C	Solvents[b]	Catalyst/mol%	Time/h	Yields[c]/%
1	CsOH/6	120	1.5/1.5	8	12	98.6
2	KOH/6	120	1.5/1.5	8	12	98.7
3	NaOH/6	120	1.5/1.5	8	12	97.1
4	KOH/6	100	1.5/1.5	8	12	8.3
5	KOH/4	120	1.5/1.5	8	12	85.8
6	NaOH/4	120	1.5/1.5	8	12	94.0
7	KOH/3	120	1.0/1.0	8	12	15.2
8	NaOH/3	120	1.0/1.0	8	12	50.1
9	NaOH/3	120	1.5/1.5	8	12	42.8
10	NaOH/4	110	1.5/1.5	8	12	24.4
11	NaOH/4	100	1.5/1.5	8	12	6.5
12	NaOH/4	90	1.5/1.5	8	12	N.D.
13	NaOH/4	120	3.0/0	8	12	14.6
14	NaOH/4	120	2.5/0.5	8	12	20.0
15	NaOH/4	120	2.0/1.0	8	12	58.5
16	NaOH/4	120	1.0/2.0	8	12	42.2
17	NaOH/4	120	0.5/2.5	8	12	18.3
18	NaOH/4	120	0/3.0	8	12	N.D.
19	NaOH/4	120	1.5/1.5	6	12	96.2
20	NaOH/4	120	1.5/1.5	4	12	95.0
21	NaOH/4	120	1.5/1.5	2	12(24)[d]	43.1(50.9)[d]
22	NaOH/4	120	1.5/1.5	0	12	N.D.
23	NaOH/4	120	1.5/1.5	4	12	95.5[e]

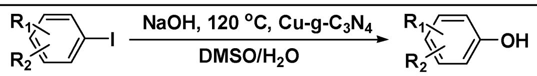
[a] All reactions were performed using 1.0 mmol of iodobenzene. [b] DMSO/mL:H_2O/mL. [c] GC yield based on the added iodobenzene, using 1,4-dioxane as internal standard. [d] Data in parentheses indicate 24 h and its corresponding yield. [e] Under an Ar atmosphere.

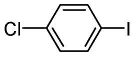
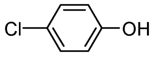
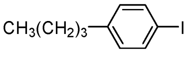
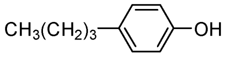
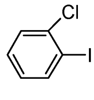
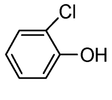
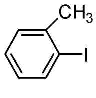
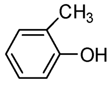
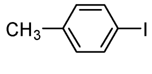
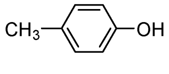
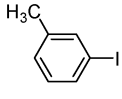
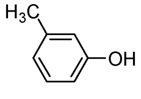
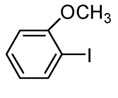
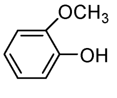
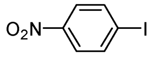
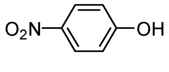
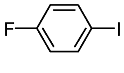
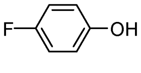
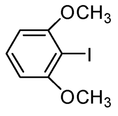
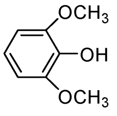
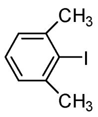
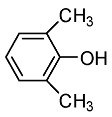
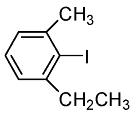
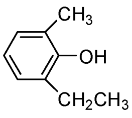
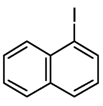
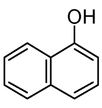
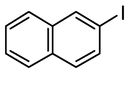
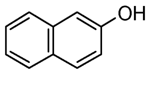
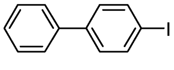
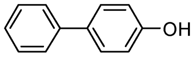
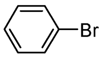
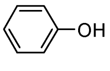
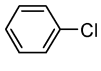
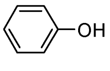
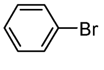
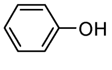
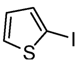
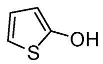
The catalytic performance of the catalytic system was further investigated using a wide range of aryl iodides as the substrates and NaOH as the base, and the results are listed in Table 2. The cross-coupling reactions of aryl iodides with NaOH proceeded very smoothly at 120 °C under an air atmosphere to afford the corresponding coupling products in good to excellent yields. For the substrates with various electron-donating and electron-withdrawing groups such as –Cl, –CH_3, –$CH_2CH_2CH_2CH_3$, –OCH_3, –Ph, –F and –NO_2, satisfactory yields of the desired phenols were obtained (Table 2, entries 1–9 and 15). Even when using the substrates bearing strong donating groups, such as two –OCH_3 groups, the reaction also proceeded efficiently to afford the corresponding coupling product in 85% isolated yields (Table 2, entry 10). The reactions of 2,4-dimethoxy-1-iodobenzene, 2,4-dimethyl-1-iodobenzene, and 3-ethyl-2-iodotoluene with NaOH, which are sterically hindered, provided high yields of the desired coupling products (Table 2, entries 10–12).

Besides, bulky 1-iodonaphthalene and 2-iodonaphthalene were also successfully converted into their corresponding phenols in excellent isolated yields (Table 2, entries 13 and 14). The results demonstrated that the steric effect did not affect the catalytic reactions significantly. We also carried out the reactions using 1-chloro-4-iodobenzene and 4-fluoroiodobenzene as the reactants, and the –Cl and –F groups were untouched in the reactions (Table 2, entries 1 and 9). To examine the scope of the title reaction, we investigated the reactions using bromobenzene, chlorobenzene and 2-iodine thiophene as the substrates under the optimized reaction conditions. The results are listed in Table 2 (entries 16–19). As shown in Table 2, in our catalytic system, aryl bromides and chlorides were inert under the experimental conditions giving no cross-coupling products (Table 2, entries 16 and 17). However, when 2 eq. of KI was added, bromobenzene can be converted to the product in moderate yield (Table 2, entry 18). Heteroaryl iodides, such as 2-iodine thiophene, also cannot work (Table 2, entry 19). Thus our catalytic system provides a highly selective coupling reaction of aryl iodides with NaOH under practical air conditions, while the –F and –Cl groups are tolerated.

The stability and reusability of the Cu-g-C_3N_4 catalyst were investigated using the coupling reaction of iodobenzene with NaOH. The results showed that the catalyst could be reused at least 5 times without a decrease in catalytic activity and selectivity (Fig. 1). More importantly, we successfully carried out a 10 g scale reaction here. Iodobenzene (10.2 g, 50 mmol), NaOH (8.0 g, 200 mmol, 4 eq.)

Table 2 Hydroxylation of aryl iodides catalyzed by Cu-g-C_3N_4 in DMSO aqueous solution[a]



Entry	Aryl halides	Time/h	Products	Yields[b]/%
1		12		83
2		12		83
3		16		78
4		16		84
5		16		89
6		16		83
7		16		80
8		12		89
9		12		82
10		16		85
11		16		89
12		16		80
13		16		79
14		16		82
15		12		93
16		12		0
17		12		0
18[c]		12		47
19		12		0

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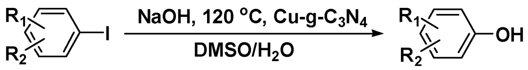

[a] Reactions were carried out with 1.0 mmol of aryl iodides, 4 mol% of Cu-g-C_3N_4, 4 eq. of NaOH, 1.5 mL DMSO and 1.5 mL H_2O at 120 °C under air conditions. [b] Isolated yields based on the added aryl iodides. [c] 2 eq. of KI was added.

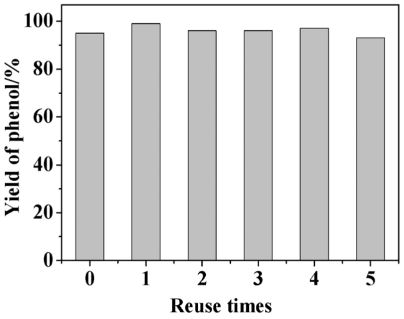

Fig. 1 The reusability of the Cu-g-C_3N_4 catalyst. Reactions were carried out with 1.0 mmol of iodobenzene, 4 mol% of Cu-g-C_3N_4, 1.5 mL DMSO and 1.5 mL H_2O at 120 °C under air conditions. Phenol yields were determined by GC.

and Cu-g-C_3N_4 (0.55 g, 2.9 mol%) were stirred in 60 mL of DMSO/H_2O (1 : 1 in volume) at 120 °C under air conditions. Complete conversion of iodobenzene was achieved after 20 h and the phenol was confirmed as the sole product by GC with 98.8% yield, demonstrating the suitability of this protocol in large-scale application.

The Cu-g-C_3N_4 catalyst was characterized systematically (Fig. S1–S5, ESI†). XRD patterns in Fig. S1 (ESI†) showed that the Cu-g-C_3N_4 catalyst exhibited the structure of g-C_3N_4.[25] No diffraction peaks of copper species were observed in the pattern. The presence of the copper species in Cu-g-C_3N_4 was confirmed by XPS analysis. The high resolution Cu2p XPS spectrum of the sample in Fig. S2b (ESI†) showed two main peaks located at about 952.5 eV and 932.3 eV corresponding to Cu2p1/2 and Cu2p3/2, respectively,[26] which indicate the existence of Cu^+ species in the catalyst. The characteristic mode of the triazine units (C_6N_7) at 810 cm^{-1} (ref. 24*c*) is also observed in the FT-IR spectra in Fig. S3 (ESI†), indicating the presence of a typical structure of g-C_3N_4. Thermogravimetric analysis of Cu-g-C_3N_4 in Fig. S5 (ESI†) illustrated that the Cu-g-C_3N_4 catalyst can bear high temperature up to 600 °C.

The reasons for the high activity and recyclability of the Cu-g-C_3N_4 catalyst might partially originate from the special structure and properties of the support. Schnick[27] and Arne Thomas[28] reported that primary and secondary amines were present at the surface of g-C_3N_4. Here in our catalytic system, the secondary amines at the surface of the catalyst probably act as a ligand of Cu^+ species to promote the reaction. Besides as the support and the stabilizer for the Cu^+ species, g-C_3N_4 also acted as the reducing agent[29] during the catalyst preparation process, leading to the formation of Cu^+ species from the $Cu(NO_3)_2$ precursor. Further exploration of the catalytic mechanism is currently under investigation in our laboratory.

In summary, we have carried out the synthesis of heterogeneous copper-catalyzed phenols without additional ligands under air conditions. The cross-coupling reactions of various aryl iodides with NaOH proceeded very smoothly with a low Cu amount (4 mol%) at 120 °C in air to afford the corresponding coupled products in good to excellent yields. The Cu-g-C_3N_4 catalyst can be reused at least 5 times without a decrease in catalytic efficiency. Phenol can be successfully produced with 98.8% yield under the experimental conditions of the 10 g scale. The catalyst is easily prepared using cheap raw materials, and is air and moisture-tolerant, stable and recyclable. Thus, the Cu-g-C_3N_4 catalyzed hydroxylation of aryl iodides shows great potential in application for synthesizing substituted phenols.

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