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CuI Nanoparticles for C−N and C−O Cross Coupling of Heterocyclic Amines and Phenols with Chlorobenzenes

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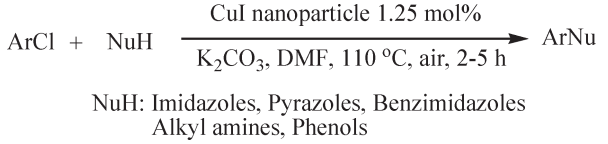
Received July 10, 2009



Employing CuI nanoparticles as an efficient catalyst for the cross-coupling reactions of various N/O nucleophilic reagents with aryl chlorides could be successfully carried out under mild conditions in the absence of both the ligands and strong bases. A variety of products including *N*-arylimidazoles and aryl ethers were synthesized in good to excellent yields.

N-Arylimidazoles and aryl ethers are valuable compounds widely employed in organic synthesis, pharmaceutical, and biological areas.[1] The development of a mild and highly efficient method for synthesis of *N*-arylazoles over classical Ullman type,[2] or nucleophilic aromatic substitution reactions,[3] or coupling with organometallic reagents[4] has recently gained considerable attention in synthetic chemistry.[5] Due to the economic attractivness of copper[6] and by using some special ligands such as N,N- and N, O-bidentate compounds, many CuI-catalyzed C−N,[7] C−O,[8] C−S,[9] and C−C[10] bond formation reactions have led to a resurgence of interest in carbon−heteroatom coupling reactions, and their applications seem to be of more and more importance.[11,12] Despite significant progress in the Cu-catalyzed *N*/*O*-arylation with aryl halides, only a few reports have appeared describing the couplings of imidazoles and/or phenols with aryl chlorides/bromides or of functional substrates or of hindered substrates[13,14] without the recovery of catalyst. Therefore, it is important to develop more simple and efficient catalytic systems for the cross-coupling methodology with an ability to utilize inexpensive aryl chlorides[15] with reusability of catalyst, and some of these have emanated from our own laboratories.[16]

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DOI: 10.1021/jo901462g Published on Web 09/22/2009

TABLE 1. Screening of Bases and Solvents for *N*-Arylation of Imidazole with *p*-Chloroanisole[a]

entry	copper (mol %)	base	solvent	time (h)	yield (%)
1	CuI (1.25)	Cs_2CO_3	1,2-dioxane	12	12
2	CuI (2.5)	Cs_2CO_3	DMSO	12	26
3	CuI (1.25)	K_3PO_4	NMP	12	36
4	CuO (np (2.5))	Cs_2CO_3	DMSO	12	36
5	CuO (np (2.5))	Cs_2CO_3	DMF	10	52
6	CuI (np (2.5))	K_3PO_4	DMF	9	61
7	(2.5)	KO *t*-Bu	DMF	8	32
8	(2.5)	Et_3N	DMF	9	41
9	(2.5)	K_2CO_3	DMF	6	95
10	(2.5)	K_2CO_3	DMF	5	95
11	(1.5)	K_2CO_3	DMF	5	95
12	(1.25)	K_2CO_3	DMSO	5	86
13	(1.25)	K_2CO_3	NMP	5	79
14	(1.25)	K_2CO_3	DMF	5	95, 94[b]
15	(1.0)	K_2CO_3	DMF	8	63

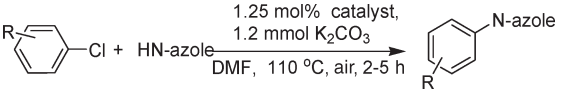
[a]Reaction conditions: imidazole (1.2 mmol), *p*-chloroanisole (1.0 mmol), catalyst (1.25 mol %), K_2CO_3 (1.2 mmol), and DMF (1 mL) were stirred for an appropriate time at 110 °C. [b]Yield after fifth cycle. np = nanoparticles.

Nanotechnology has been one of the most active research areas in recent years. In this area, preparation of nanomaterials is the foundation for the development of nanoscience and nanotechnology.[17] For high catalytic activity, colloidal metal nanoparticles have been widely used in organic synthesis.[18] Recently, nano CuO was used as an active catalyst for carbon−heteroatom coupling.[19] Nano CuI is a new functional material prospective in fields like chemical fibers, polymers, catalysts, and semiconductors.[20]

Herein, we wish to report "sodium citrate" assisted CuI nanoparticle synthesis and its application as an efficient catalyst for *N*/*O*-arylation of amines and phenols with chloroarenes. To test the efficiency of the catalytic activity, we chose to focus our initial studies on the cross coupling of imidazoles/phenols through the use of *p*-chloroanisole as model arylating agent without use of any additional chelating ligand. Further, the reaction conditions were optimized on the basis of the catalysts, bases, and solvents at 110 °C for carbon−heteroatom bonding. We noticed with decreasing basicities, Cs_2CO_3, K_3PO_4, and K_2CO_3 led to a sharp increase in efficient *N*-arylation of imidazole (Table 1, entry 9). Of all the solvents screened, DMF served as the prime solvent; DMSO and NMP were fair solvents but were not as good as DMF. The optimized conditions employed were 1.25 mol % of catalyst and 1.2 mmol of K_2CO_3 in 1 mL of DMF (see Table 2 in the Supporting Information for optimization of *O*-arylation).

We chose a variety of structurally divergent chlorobenzenes possessing a wide range of functional groups to understand the scope and generality of the CuI nanoparticle-promoted *N*-arylation of imidazoles, and the results are summarized in Table 2. It is observed that the coupling follows the sequence ArI > ArCl, and aryl fluorides were generally found to be inert to this reaction (Table 2, entry 1). Chlorobenzenes having electron-donating (ED) groups (Table 2, entries 2 and 3) showed less reactivity in comparison to those with electron-withdrawing (EW) groups (Table 2, entries 4−13).

TABLE 2. *N*-Arylation of Imidazoles with Chlorobenzenes[a]



entry	R	HN-Azole	time (h)	yield (%)
1	4-X (2a)	(1a)	4 16	X = I, 95 = Cl, 56
2	4-CH_3 (2b)	1a	14	36
3	4-OCH_3 (2c)	1a	5	95
4	4-NO_2 (2d)	1a	3	95
5	2-NO_2 (2e)	1a	2	99, 97[b]
6	4-CN (2f)	1a	4	65
7	2-CN (2g)	1a	2	87
8	4-CHO (2h)	1a	2	87
9	2-CHO (2i)	1a	6	99
10	4-Cl (2j)	1a	3	95
11	4-Br Cl = I (2k)	1a	1	99
12	4-CF_3 (2l)	1a	5	95
13	4-$COCH_3$ (2m)	1a	5	99

[a]Reaction conditions: imidazole (1.2 mmol), aryl chlorides (1.0 mmol), catalyst (1.25 mol %), K_2CO_3 (1.2 mmol), and DMF (1 mL) were stirred for an appropriate time at 110 °C. [b]Yield after fifth cycle.

The chelating groups at the *ortho* position also showed a pronounced affect in increasing the *N*-arylated yield with a decrease in reaction times (Table 2, entries 5 vs 4, 7 vs 6, and 9 vs 8). No side products such as anisole or polyalkylation of dihalosubstituted benzenes were observed in the *N*-arylation of imidazole (Table 2, entry 10 and 11), and the selectivity of 1-phenyl-1*H*-imidazole is >99%. When two different halide groups are present (Table 2, entry 11), it is observed that the coupling takes place selectively at the C−I bond over the C−Br bond.

Various other substituted azoles such as pyrazoles, benzimidazoles, and primary and secondary aliphatic cyclic amines were also successfully coupled with chlorobenzenes to afford

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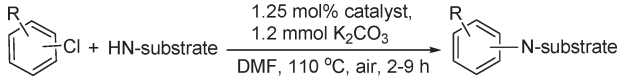
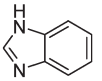
TABLE 3. ***N*-Arylation of Pyrazoles, Benzimidazoles, Pyrrole, and Alkylamines with Chlorobenzenes**[a]



entry	aryl chloride	NH-substrate	time (h)	yield (%)
1	2c	(1b) 	4	90
2	2c	(1c) 	9	78
3	2c	(1d) 	6	90
4	2l	1d	4	95
5	2d	(1e) 	5	95
6	2c	(1f) 	7	95
7	2d	(1f)	2	95
8	2j	(1f)	2	97
9	2n	(1g) 	3	99
10	2o	(1g)	3	98

[a]Reaction conditions: NH-substrate (1.2 mmol), aryl chlorides (1.0 mmol), catalyst (1.25 mol %), K_2CO_3 (1.2 mmol), and DMF (1 mL) were stirred for an appropriate time at 110 °C. Entries 9 and 10, **2n** = 3-nitrochlorobenzene and **2o** = 4-chlorobenzoic acid.

N-arylated products in good to excellent yields (Table 3, entries 1−10).

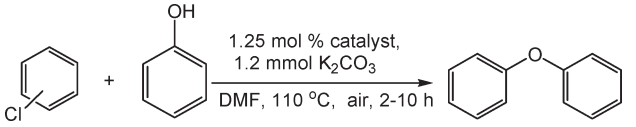
Among the azoles, pyrazoles, pyrrole, and benzimidazoles reacted equally well with substituted chlorobenzenes to yield the corresponding *N*-arylated products in good yields (Table 3, entries 1−4). Unfortunately, the reactions seemed to be sensitive to steric hindrance on the nucleophilic reagent, and 1*H*-benzimidazole seemed to be more difficult to react with aryl chloride compared to imidazole (Table 3, entry 2). It is noteworthy to observe that when the reaction was conducted in the absence of air there was no coupled product which clearly emphasized that the process involves oxidative addition followed by reductive elimination. A detailed mechanistic study on the role of air in this reaction is under progress.

On the basis of the optimized reaction conditions (see Table 2, Supporting Information), we explored the catalytic efficiency of CuI nanoparticles in the *O*-arylation of phenol with various functionalized chlorobenzenes, and the results are summarized in Table 4.

As can be seen from Table 4, most of the tested substituted chlorobenzenes afforded the corresponding diaryl ethers in good to excellent yields (Table 4, entries 2−10). The reaction conditions were compatible with a variety of functionalized aryl chlorides, including those bearing electron-donating and electron-withdrawing groups (Table 4, entries 2−10).

To further reveal the scope of CuI nanoparticles catalyzed in *O*-arylation reaction, various substituted phenols were reacted with various substituted aryl chlorides (Table 5, entries 1−5). Reaction of *p*-nitrochlorobenzene with *p*-bromophenol afforded *O*-arylated product in excellent yield (Table 5, entry 1).

TABLE 4. ***O*-Arylation of Phenols with Chlorobenzenes**[a]



entry	R	product	time (h)	yield (%)
1	X	PhOPh	10	X = Cl, 47
			8	X = Br, 72
			2	X = I, 98
2	4-CH_3	4-CH_3PhOPh	8	57
3	2-CH_3	2-CH_3PhOPh	10	33
4	4-OCH_3	4-OCH_3PhOPh	5	80, 78[b]
5	2-OCH_3	2-OCH_3PhOPh	5	90
6	4-NO_2	4-NO_2PhOPh	4	95
7	2-NO_2	2-NO_2PhOPh	2	98
3	3-CN	3-CNPhOPh	4	93
9	4-$COCH_3$	4-$COCH_3$PhOPh	3	98
10	4-Cl	4-ClPhOPh	2	98

[a]Reaction conditions: phenol (1.2 mmol), aryl chlorides (1.0 mmol), catalyst (1.25 mol %), K_2CO_3 (1.2 mmol), DMF (1 mL) were stirred for appropriate time at 110 °C. [b]Yield after fifth cycle.

To test the versatility of this catalyst in the present cross-coupling reaction, we chose the reaction between *p*-nitrophenol and *p*-chloroanisole since the *para*-substituted electron-rich aryl halides are difficult substrates for the corresponding transformations (Table 5, entry 2).

We were pleased to notice that *p*-nitrophenol, which has been usually unreactive in several copper-catalyzed *O*-arylation reactions with aryl halides,[21] conferred excellent yields with CuI nanoparticles (Table 5, entry 2). Both electron-donating substituents on aryl chlorides and electron-withdrawing substituents on phenols afforded the corresponding coupling products with insignificant decrease in yields compared with electron-withdrawing substituents on aryl chlorides (Table 5, entries 2 and 5). This shows that this catalytic system is relatively insensitive to electronic effects of substituent on coupling partners for C−O bond formation. On the other hand, chlorobenzene did not react with 2-naphthol (Table 5, entry 6); this may be due to the steric hindrance of phenyl group.

The possible mechanism for *N*- and *O*-arylation is outlined in Scheme 1. We believe that the reaction may occur via oxidative addition followed by reductive elimination.[19] Stabilization of the well-dispersed CuI nanoparticles by DMF[22] and amine/alcohol may lead to an active cluster intermediate **2** which may undergo oxidative addition with aryl halide to give intermediate **3** where the positive charge developed may be shared among the CuI nanoparticles present on the surface of the cluster. The intermediate **3** may transform to **1** by reductive elimination providing C-heteroatom cross-coupled product followed by the removal of hydrogen chloride with base.

Transmission electron microscope (TEM) studies of both fresh and used catalysts were carried out to understand the

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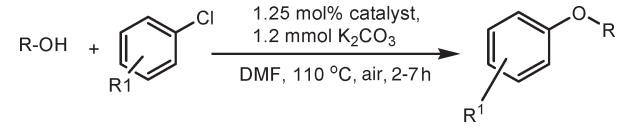
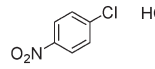
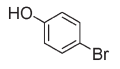
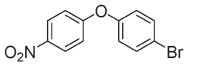
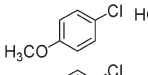
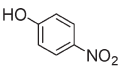
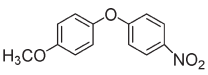
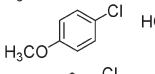
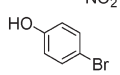
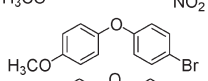
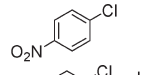
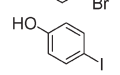
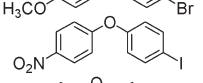
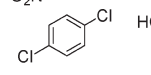
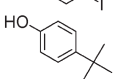
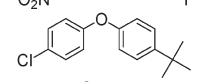
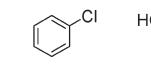
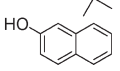
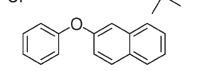
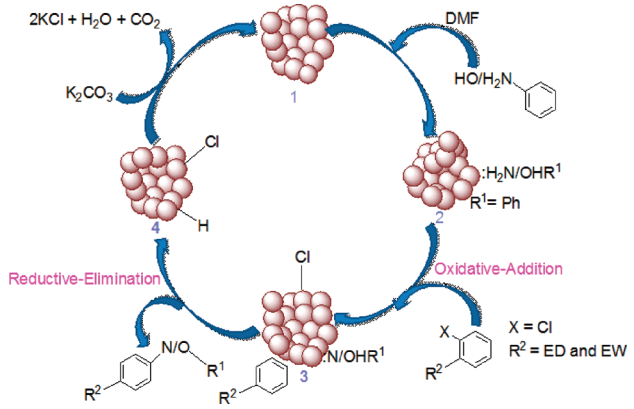
TABLE 5. *O*-Arylation of Substituted Phenols with Substituted Chlorobenzenes[a]



entry	aryl chlorides	phenols	product	time (h)	yield (%)
1				2	98
2				5	91
3				4	99
4				2	99
5				2	98
6				7	n.r

[a]Reaction conditions: phenol (1.2 mmol), aryl chlorides (1.0 mmol), catalyst (1.25 mol %), K_2CO_3 (1.2 mmol), and DMF (1 mL) were stirred for an appropriate time at 110 °C.

SCHEME 1. Possible Mechanism for N/O-Arylation



shape and size of the particles. Parts a and b of Figure 1 show the TEM images of the fresh and the used catalyst after fifth cycle, respectively. Interestingly, it is observed that the shape and size of the particles remain unchanged and supports the assumption that the morphology of the catalyst remains the same even after recycling. The complete characterization of catalyst is provided in the Supporting Information.

Furthermore, the catalytic system can be reused for several cycles without loss of its activity (Table 2, entry 5; see Table 3 and Figure S4, Supporting Information). The true heterogeneity of the catalyst was examined when the reaction was discontinued during the first half of its reaction time, the filtrate (solid catalyst was removed by filtration) was stirred for the next half reaction time, and no coupling reaction occurred, which clearly indicates that the reaction does not proceed devoid of active catalyst.[23]

(23) Pachón, L. D.; Rothenberg, G. *Appl. Organomet. Chem.* **2008**, *22*, 288.

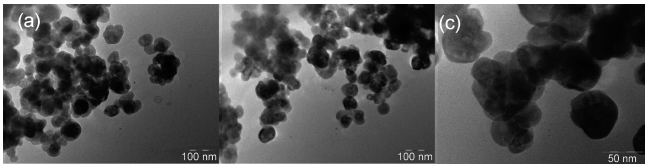


FIGURE 1. TEM images: (a) fresh porous CuI nanoparticles; (b) CuI nanoparticles after fifth cycle; (c) CuI nanoparticles at 50 nm.

In conclusion, we have developed an efficient, inexpensive, and environmentally benign catalyst system for the efficient carbon−heteroatom coupling, showing C−N and C−O bond formation of a variety of amines and phenols under ligand-free conditions at relatively mild conditions. Although we previously reported the Cu-catalyzed arylation of benzimidazole and imidazole,[16c] the present work is an improved procedure for these heterocycles that obviates the need of the high stoichiometric amounts of Cu catalyst with aryl chlorides. This recyclable catalyst offers several advantages, including simplicity of operation, easy workup, and high yields.

Experimental Section

General Procedure. An oven-dried 25 mL round-bottomed flask with a magnetic stirring bar was charged with CuI nanoparticles (1.25 mol %), K_2CO_3 (0.1662 g, 1.2 mmol), nitrogen-containing heterocycle (1.2 mmol)/phenol (1.2 mmol), aryl chloride (1.0 mmol), and DMF (1 mL) under air. The reaction mixture was stirred for 30 min at room temperature and then transferred to a preheated oil bath at 110 °C. At the end of the reaction, as judged by TLC, the reaction mixture was then cooled to room temperature, diluted with 2−3 mL of EtOAc, and centrifuged to remove the catalyst, and the catalyst was further washed with 5−10 mL of EtOAc to make it free from organic matter. The combined organic extracts were then concentrated under reduced pressure, and the resulting residue was purified by column chromatography on silica gel (60−120) using hexane/ethyl acetate (80:20) eluent to provide the desired *N*-arylated/*O*-arylated product. The catalyst was oven-dried at 65 °C for 2 h and reused.

1-(2-Nitrophenyl)-1*H*-imidazole (Table 2, Entry 5). Thick orange liquid, 99%. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 6.82 (t, J = 7.9, 8.7 Hz, 2H), 7.02 (d, J = 8.7 Hz, 2H), 7.40 (t, J = 8.7 Hz, 2H), 7.60−7.78 (dd, J = 7.9, 1.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO, ppm): δ 120.5, 121.1, 123.9, 127.4, 131.6, 132.4, 135.7, 138.4, 144.2. EI-MS: m/z = 189 (M^+). Anal. Calcd for $C_9H_7N_3O_2$: C, 57.14; H,3.73; N, 22.21. Found: C, 57.12; H, 3.69; N, 22.18.

1-(4-Nitrophenoxy)-4-methoxybenzene (Table 5, Entry 2). Off-white solid, yield 91%. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 3.85 (s, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 10.3 Hz, 2H), 7.15 (d, J = 8.8 Hz, 2H), 8.15 (d, J = 8.1 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$+ DMSO, ppm): δ 55.9, 113.8, 118.5, 118.6, 120.5, 141.6, 149.4, 153.8, 163.3. EI-MS: m/z = 245 (M^+). Anal. Calcd for $C_{13}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 63.71; H, 4.49; N, 5.70.

Acknowledgment. R.A. thanks GAP-0152, Department of Science and Technology (DST-India), for a research fellowship.

Supporting Information Available: General experimental procedures, catalyst preparation, and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.