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Highly efficient copper catalytic system for the O-arylation of phenol with iodoarene

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ABSTRACT

An efficient Cu-catalyzed O-arylation was carried out by involving phenols with iodoarenes to afford various substituted diarylether derivatives with tiny loading of Cu_2O and 1*H*-imidazole-4-carboxylic acid as catalytic system under mild conditions, which provided good to excellent yields with good tolerance of functional groups.

Diaryl ether derivatives are very important compounds for organic synthesis because of their wide application in biology,[1] polymer science[2] and the synthesis of natural products;[3] most of them are prepared by the transition-metal-catalyzed O-arylation of phenol with aryl halide. Among the various protocols reported to date, the copper catalyzed O-arylation is the most general pathway to generate diaryl ethers. Copper catalyzed Ullmann reaction[4] involving the coupling of phenols with aryl halides is a convenient method for large scale synthesis under aerobic conditions. However, they were always performed with high catalyst loadings[5] or requirement of high temperatures[6] which inhibited their application for the construction of complex molecules.[7,8] The most effective modification for this Ullmann-type O-arylation is generally by ligand screening. Thus, many efficient ligands were introduced to promote the coupling reaction, including amine,[9] triol,[10] 1,10-phenanthroline,[11] bipyridine,[11] amino acid[12] and phosphoric acid etc.[13]

It was revealed by recent reports that the Ullmann-type O-arylation could be carried out under mild conditions.[14] However, the loading of catalyst for most cases was still high,[15] which repressed the economic consideration of industry. Therefore, a better combination of copper source with ligand was necessary for improvement of the performance of this coupling reaction. Herein, we wish to publish an efficient method with the effective combination of Cu_2O with amino acid species as the catalytic system for O-arylation of phenols with iodoarenes, which require only small amount of catalyst and mild conditions to generate a wide range of diaryl ethers.

In a preliminary reaction, iodobenzene (**1a**) was treated with phenol (**2a**) in the presence of 10 mol CuI, 20 mol % 2,2′-bipyridine (**L1**) and 2.0 equiv K_3PO_4 in DMF at 100 °C for 24 h; the corresponding diphenylether was obtained only in a 5% NMR yield (Table 1, entry 1). Almost all of the starting materials were maintained under the above condition, thus made us try to find the suitable ligand out in our first investigation.

During the study of the effect of ligands, we discovered that when the 1,10-phenanthroline (**L2**) and 2,2′-biimidazole (**L3**) were employed as ligands, the desired product **3a** was obtained in 8% and 11% yields, respectively, (entries 2 and 3). **L4** and **L8** were found to be functionless, only amino acid species (Table 1, entries 5–7) significantly enhanced yields of the product **3a**. The best choice of the ligand was **L6** (entry 6), which provided higher yield than others.

With a suitable ligand in hand, we further optimized the reaction conditions and the results are listed in Table 2. It was found that only polar solvent afforded desired product **3a** (Table 2, entries 1–7), DMF and DMAc were better than others. The CH_3CN provided slightly lower yield; however, it was chosen because of the easy removable property. The performance of this coupling reaction also strongly depends on the base (entries 8–10); the Cs_2CO_3 exhibited better improvement than K_2CO_3 and K_3PO_4 to give the corresponding product **3a** in a 79% yield. *t*-BuOK showed no reactivity for this reaction. When different copper sources were employed, the reaction was also affected (entries 11–15); among the various copper sources employed as catalyst, the Cu_2O was found to be the most

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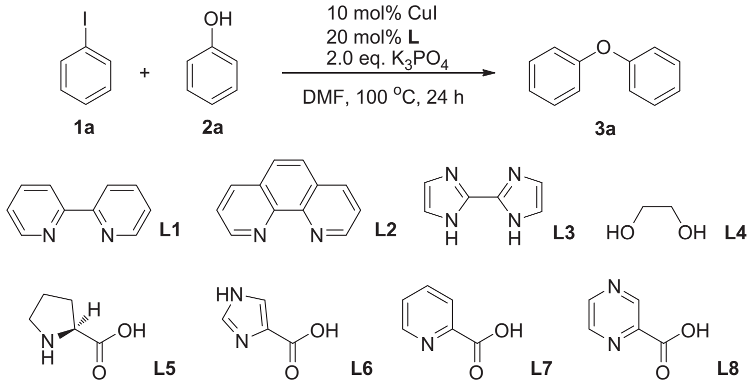
Table 1
Comparison of various ligands in the coupling reaction[a]

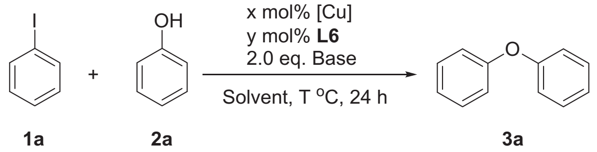


Entry	L	Yield[b] (%)
1	**L1**	5
2	**L2**	8
3	**L3**	11
4	**L4**	0
5	**L5**	44
6	**L6**	59
7	**L7**	53
8	**L8**	0

[a] Reactions were carried out using 0.1 mmol iodobenzene (**1a**), 0.12 mmol phenol (**2a**) with 10 mol % CuI, 20 mol % ligand and 2.0 equiv K_3PO_4 in 1.0 mL DMF for 24 h.

[b] ^1H NMR yield based on internal standard mesitylene.

Table 2
Optimization of reaction conditions[a]



Entry	x	y	[Cu]	Solvent	base	T (°C)	Yield[b] (%)
1	10	20	CuI	DMF	K_3PO_4	100	59
2	10	20	CuI	Dioxane	K_3PO_4	100	28
3	10	20	CuI	Benzene	K_3PO_4	100	0
4	10	20	CuI	Toluene	K_3PO_4	100	0
5	10	20	CuI	DMAc	K_3PO_4	100	59
6	10	20	CuI	DME	K_3PO_4	80	23
7	10	20	CuI	CH_3CN	K_3PO_4	80	52
8	10	20	CuI	CH_3CN	*t*-BuOK	80	0
9	10	20	CuI	CH_3CN	K_2CO_3	80	62
10	10	20	CuI	CH_3CN	Cs_2CO_3	80	79
11	10	20	CuBr	CH_3CN	Cs_2CO_3	80	67
12	10	20	$Cu(OAc)_2$	CH_3CN	Cs_2CO_3	80	62
13	10	20	$Cu(OTf)_2$	CH_3CN	Cs_2CO_3	80	81
14	10	20	CuSCN	CH_3CN	Cs_2CO_3	80	67
15	10	20	Cu_2O	CH_3CN	Cs_2CO_3	80	93
16[c]	5	10	Cu_2O	CH_3CN	Cs_2CO_3	80	96
17[c]	5	5	Cu_2O	CH_3CN	Cs_2CO_3	80	93
18[c]	5	5	Cu_2O	CH_3CN	Cs_2CO_3	60	75
19[c]	5	5	Cu_2O	CH_3CN	Cs_2CO_3	rt	5
20[c]	1	2	Cu_2O	CH_3CN	Cs_2CO_3	80	93

[a] Reactions were carried out using 0.1 mmol iodobenzene (**1a**), 0.12 mmol phenol (**2a**) with copper source, ligand and 2.0 equiv base in 1.0 mL solvent for 24 h (under air).

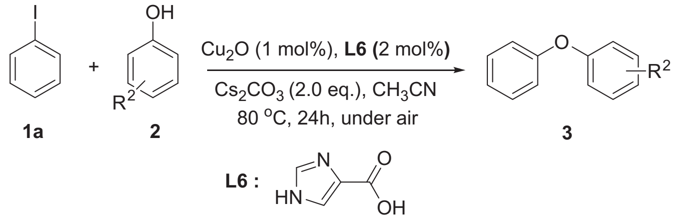
[b] ^1H NMR yield based on internal standard mesitylene.

[c] 0.05 mL solvent.

effective copper source to increase the yield of **3a** (entry 15). Higher concentration (entries 16–20) was helpful for decreasing the loading of catalyst to only 1.0 mol % Cu_2O with 2.0 mol % ligand. In addition, lower temperature significantly reduced the yield of desired product or made the reaction inert (entries 18–19). No desired product was obtained without employment of **L6**.

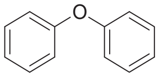
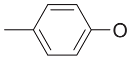
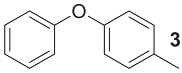
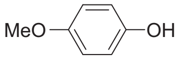
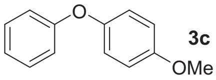
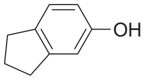
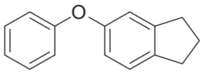
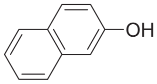
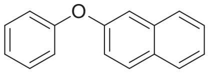
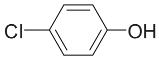
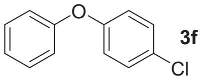
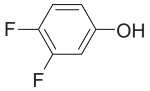
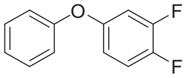
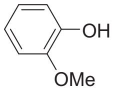
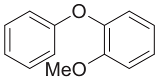
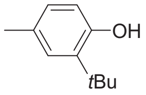
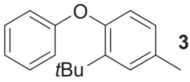
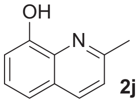
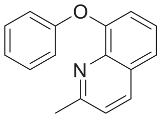
The Cu-catalyzed O-arylation was successfully extended to various substituted phenols (**2**) with iodobenzene (**1a**); the results are

Table 3
Copper-catalyzed O-arylation of phenols with iodobenzene[a]



1a **2** **3**

L6 :

Entry	2	3	Yield[b] (%)
1	**2a**	 **3a**	93
2	 **2b**	 **3b**	95
3	 **2c**	 **3c**	99
4	 **2d**	 **3d**	96
5	 **2e**	 **3e**	85
6	 **2f**	 **3f**	79
7	 **2g**	 **3g**	81
8	 **2h**	 **3h**	99
9	 **2i**	 **3i**	94
10	 **2j**	 **3j**	76

[a] Reactions were carried out using 0.5 mmol iodobenzene (**1a**), 0.6 mmol phenol (**2**) with 1 mol % Cu_2O, 2 mol % **L6** and 2.0 equiv Cs_2CO_3 in 0.25 mL CH_3CN for 24 h (under air).

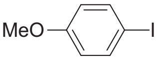
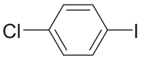
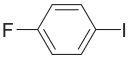
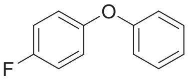
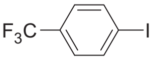
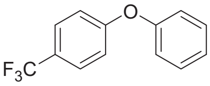
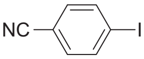
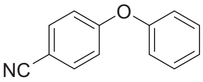
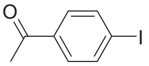
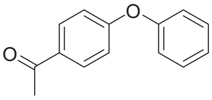
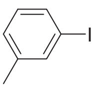
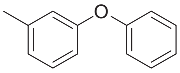
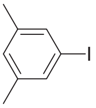
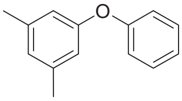
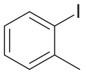
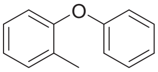
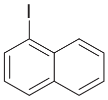
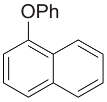
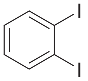
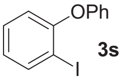
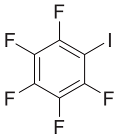
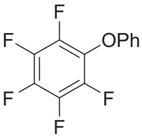
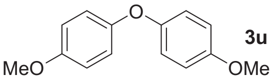
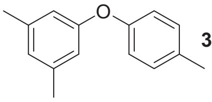
[b] Isolated yield after column chromatography.

listed in Table 3. An electron-donating group at the *para*-position of phenols reacted with iodobenzene in the presence of 1 mol % Cu_2O, 2 mol % **L6** and Cs_2CO_3 (2 equiv) in acetonitrile to give the corresponding diarylethers in excellent yields (Table 3, entries 2–4). Under the same reaction conditions, 2-naphthol and para electron-withdrawing groups also reacted well but gave slightly lower yields (entries 5–7). The *ortho*-substitutes on the phenol did not display effective steric effect to reduce the yields. Thus, the *ortho*-substituted phenols **2h** and **2i** provided the corresponding products **3h** and **3i** in 99% and 94% yields, respectively, (entries 8–9). The 8-hydroxyquinoline derivative performed well for this reaction but only with a good yield of 76% probably due to the formation of a five-membered copper complex (entry 10).

By using the same protocol, we were also able to carry out the C–O coupling reaction of phenol with various substituted iodoarenes (Table 4). The 4-tolyliodide reacted smoothly with phenol to give the corresponding product **3b** in a 92% yield (entry 1), however, a strong electron-donating group at the *para*-position of iodobenzene significantly inhibited the coupling reaction due to the sluggish oxidative addition of Cu complex to **1c** (entry 2).

Para electron-withdrawing group provided very good yields except **1f** (entries 3–7). *Meta*-substituted iodoarenes also well reacted to phenol and afforded the corresponding diarylethers **3o** and **3p** in excellent yields (entries 8–9); however, a methyl group at the *ortho*-position of iodoarene showed large hindrance to retard the oxidative addition of Cu complex (entry 10) and gave only moderate yield. 1-Naphthyliodide (**1l**) provided the corresponding product **3r** in only a 32% yield (entry 11). 1,2-diiodobenzene (**1m**) reacted with phenol to afford single product **3s** in moderated yield 42%. It is noteworthy that no double O-arylation adduct was observed in this reaction (entry 12). Poly-fluoro substituted compound was also well tolerated in this coupling reaction and the product **3t** was obtained in a 64% yield (entry 13). A lot of unreacted starting materials were recovered in the cases with comparative lower

Table 4
Copper-catalyzed O-arylation of phenols with iodoarenes[a]

Entry	1	2	3	Yield[b] (%)
1	 **1b**	**2a**	**3b**	92
2	 **1c**	**2a**	**3c**	64
3	 **1d**	**2a**	**3f**	90
4	 **1e**	**2a**	 **3k**	81
5	 **1f**	**2a**	 **3l**	72
6	 **1g**	**2a**	 **3m**	95
7	 **1h**	**2a**	 **3n**	94
8	 **1i**	**2a**	 **3o**	92
9	 **1j**	**2a**	 **3p**	93
10	 **1k**	**2a**	 **3q**	51
11	 **1l**	**2a**	 **3r**	32
12	 **1m**	**2a**	 **3s**	42
13	 **1n**	**2a**	 **3t**	64
14	**1c**	**2c**	 **3u**	96
15	**1j**	**2b**	 **3v**	95

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[a] Reactions were carried out using 0.5 mmol iodoarene (**1**), 0.6 mmol phenol (**2**) with 1 mol % Cu_2O, 2 mol % **L6** and 2.0 equiv Cs_2CO_3 in 0.25 mL CH_3CN for 24 h (under air).

[b] Isolated yield after column chromatography.

yields even for double reaction time (entries 10–12), and no byproducts were observed. The combinations of various iodoarenes with phenols also generated the desired products in excellent yields (entries 14–15).

In conclusion, we have developed an effective Cu_2O/1*H*-imidazole-4-carboxylic acid catalytic condition for the O-arylation of phenols with iodoarenes. This method efficiently provided diaryl ether derivatives in moderate to excellent yields with good tolerance of various functional groups and only required very small amount of catalyst under mild conditions, thus increased the possibility for the application to industry. Further studies to extend the application of this catalytic system are currently underway.

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Supplementary data

Supplementary data (experimental procedure, ^{1}H and ^{13}C NMR spectra and spectral data for all the new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.149.

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