

Aminophenols as Efficient Ligand for Copper-Catalyzed Ullmann-type Synthesis of Diaryl Ethers

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Carbon-oxygen bonds extensively exist in all kinds of biologically active natural products, important pharmaceutical compounds and polymers.^{1,2} The palladium-catalyzed formation of carbon-oxygen bonds is one of the two major methods available for aryl ether synthesis. However, palladium-based protocols, although successful,³ have some inherent limitations such as moisture sensitivity, costly metal catalysts, and environmental toxicity. These shortcomings limit their massive applications in industrial fields, particularly in the pharmaceutical industry, where metal contamination to the products may cause serious problems. The other one is the copper-mediated Ullmann ether synthesis. The harsh classical conditions of the Ullmann ether synthesis also have limitations in its application because of the high temperatures (120–220 °C) required and the use of stoichiometric amounts of copper reagents.⁴ In the past years, significant advances have been achieved for the copper-catalyzed synthesis of diaryl ethers by use of the new ligands explored, such as 1-naphthoic acid,⁵ 8-hydroxyquinoline,^{6,7} 2,2,6,6-tetramethylheptane-3,5-dione,⁸ amino acids,^{9–11} diimine ligands,^{12,13} PPAMP,¹⁴ phosphazene P₄-*t*-Bu base,¹⁵ β -ketoester,¹⁶ 1,1'-binaphthyl-2,2'-diamine,¹⁷ tripod ligands,¹⁸ silica supported Cu(II),¹⁹ aryl boronic acid,²⁰ tetraethyl ortho-silicate (as solvent),²¹ (2-pyridyl)acetone,²² ⁿBu₄NBr (as phase transfer catalyst),²³ picolinic acid,²⁴ methenamine²⁵ and some copper(I) complexes.^{26–28} With the carefully selected combinations of a catalytic amount of copper sources, bases, and supporting ligands, aryl bromides and aryl iodides had been reported to couple with phenols with excellent yields under mild conditions. Therefore, the further discovery of new facile ligand structures for the copper-catalyzed cross-coupling reactions of phenols with aryl halides is still an area of considerable interest.

Aminophenols are a type of simple and versatile bidentate ligand, and they can be easily accessed by the reduction of the corresponding Schiff bases, which can be prepared from inexpensive and readily available starting materials. These ligand systems have been utilized in main group, transition-metal and lanthanides coordination chemistry, and some of these metal complexes show good activity in homogeneous catalysis.²⁹ To our knowledge, there are very few examples available involving it in copper-catalyzed arylation with

phenols. Herein we wish to report the efficient use of aminophenols (Figure 1) for the copper catalyzed *O*-arylation of aryl halides with phenols.

The ligands L₁–L₆ were synthesized by known literature methods (Fig. 1).³⁰ These ligands (L₁–L₆) are examined using iodobenzene and phenol as model substrates in the presence of tripotassium phosphate and copper salts at 110 °C for 24 h in DMF. The results are listed in Table 1. The desired product was obtained in 8% yields without the presence of ligand (Table 1, entry 1). L₁, with a phenyl group on the amine moiety, showed good efficiency and provided the coupling product in 75% yield (Table 1, entry 2). The results also showed that the electronic effect, the steric effect of the substituents on the ligand also had important effects on the catalyst properties. For example, L₂, with a methyl group at the ortho position of aniline, was found to be an even more efficient ligand and afforded the coupling product in 91% yields (Table 1, entry 3), but L₄ and L₆, with a larger group (*e.g.* methoxy group and isopropyl group) at the ortho position of aniline, were considerably less active under the same conditions (80% yield) (Table 1, entries 5 and 7). Meanwhile, L₃, with an anisole group, was found to be an efficient ligand and afforded the coupling product in 90% yields (Table 1, entry 4). Conversely, L₅, with 4-chlorophenyl group on the amine moiety, was less active under the same conditions (87% yield) (Table 1, entry 6).

Subsequently, L₂ was selected as the ligand for assisting Cu salts in catalyzing *O*-arylation of phenols with aryl halides to further investigate the effects of the other conditions on the *O*-arylation, including alkalis, solvents, copper salt. The results are listed in Table 2. Initially, on turning our attention to examining solvent effects at 65 °C, we find that acetonitrile as a solvent gave the best result, furnishing diphenyl ether in 60% yield. DMF, DME, THF, DMSO and 1,4-dioxane were not as good as acetonitrile (Table 2, entries 1–7). Meanwhile, Toluene was not suitable as a solvent, only

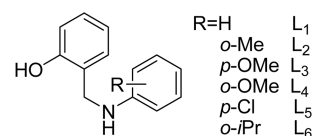


Figure 1. Structures of Ligands.

Table 1. Comparison of various ligands in the coupling reaction^a

Entry	Ligand	Yield ^b (%)	Entry	Ligand	Yield ^b (%)
1	—	8	5	L ₄	80
2	L ₁	75	6	L ₅	87
3	L ₂	91	7	L ₆	80
4	L ₃	90			

^aGeneral reaction conditions: 1.5 mmol of phenol, 1.0 mmol of iodobenzene, 2.0 mmol of K₃PO₄, 0.05 mmol CuI, 0.05 mmol ligand, 0.5 mL of anhydrous DMF. ^bIsolated yield.

Table 2. Copper-catalyzed *O*-arylation of phenol with aryl halide: optimization of the reaction conditions^a

Entry	Base	Copper salt	Solvent	Yield ^b , %
1 ^c	K ₃ PO ₄	CuI	DMF	49
2 ^c	K ₃ PO ₄	CuI	DMSO	35
3 ^c	K ₃ PO ₄	CuI	DME	45
4 ^c	K ₃ PO ₄	CuI	toluene	15
5 ^c	K ₃ PO ₄	CuI	dioxane	43
6 ^c	K ₃ PO ₄	CuI	THF	32
7 ^c	K ₃ PO ₄	CuI	CH ₃ CN	60
8	K ₃ PO ₄	CuI	CH ₃ CN	91
9	K ₂ CO ₃	CuI	CH ₃ CN	31
10	KOH	CuI	CH ₃ CN	28
11	Na ₂ CO ₃	CuI	CH ₃ CN	Trace
12	Cs ₂ CO ₃	CuI	CH ₃ CN	90
13	K ₃ PO ₄	CuCl	CH ₃ CN	91
14	K ₃ PO ₄	Cu ₂ O, (2.5%)	CH ₃ CN	48
15	K ₃ PO ₄	CuCl ₂	CH ₃ CN	77
16 ^d	K ₃ PO ₄	CuCl	CH ₃ CN	83
17 ^e	K ₃ PO ₄	CuCl	CH ₃ CN	35

^aGeneral reaction conditions: 1.5 mmol of phenol, 1.0 mmol of iodobenzene, 2.0 mmol of K₃PO₄, 0.05 mmol L₂, 0.5 mL of anhydrous DMF. ^bIsolated yield. ^cAt 65 °C. ^dBromobenzene was used in place of iodobenzene. ^eChlorobenzene was used in place of iodobenzene.

15% yield was obtained (Table 2, entry 4). After screening a series of bases, 2 equiv of K₃PO₄ was determined to be the most effective base and gave diphenyl ether in 91% yield at 81 °C (Table 2, entries 8–11). Although analogous yields (90%) were obtained when Cs₂CO₃ was used as a base, however Cs₂CO₃ is expensive (Table 2, entry 12). For comparison on the efficiency of copper salts in the *O*-arylation reactions, both CuCl and CuI were found to be highly effective, CuCl₂ was moderate, whereas Cu₂O was much less effective, which might be attributable to the low solubility of Cu₂O (Table 2, entries 8 and 13–15). As previously reported,⁴ aryl iodides displayed higher reactivity than aryl bromides and chlorides (Table 2, entries 16 and 17). Therefore, the combination of less expensive CuCl (5%), 5% L₂ and 200% K₃PO₄ in CH₃CN at 81 °C was chosen as the optimal condi-

Table 3. Cu-Catalyzed Coupling Reaction of Aryl Iodides with Phenols^a

Entry	Ar ₁	Ar ₂	Product	Yield ^b (%)
1	1a	2a	3aa	86
2	1a	2b	3ab	91
3	1b	2c	3bc	85
4	1b	2b	3bb	89
5	1b	2d	3bd	90
6	1c	2b	3cb	85
7	1d	2b	3db	92
8	1d	2d	3dd	95
9	1e	2c	3ec	92

^aUnless otherwise stated, General reaction conditions: 1.5 mmol of phenol, 1.0 mmol of ArI, 2.0 mmol of K₃PO₄, 0.5 mL of anhydrous CH₃CN under Ar atmosphere for 24 h. ^bIsolated yield.

tions for further exploration.

The scope of the copper-catalyzed C–O bond formation was explored by using a variety of aryl iodides or aryl bromides with substituted phenols under the optimized conditions. As shown in Table 3, the coupling reactions were performed well for all the aryl iodides examined with excellent yields (Table 3). As summarized in Table 4, less active aryl bromides were also successfully coupled with phenols under our optimal conditions. The results clearly revealed that an electron-withdrawing group in the aryl bromides favored the coupling reactions (Table 4, entries 24–29 vs 1–4, 10), however an electron-releasing group in the aryl bromides went against the coupling reactions. For example 4-methylbromobenzene could be coupled with phenol to give the products in 59–85% yields (Table 4, entries 11–18), yet aryl bromides with electron-withdrawing substituents, e.g. 2-acetylphenyl bromide, afforded the corresponding products in 86–95% yields (Table 4, entries 24–25, 27–28) with the exception of 4-cyanophenol, which led to a low yield (56%) for the coupling reaction (Table 4, entry 29). Furthermore, the *O*-arylation of phenols with electron-donating substituents and aryl bromides gave good to excellent product yields (61–89 %) (Table 4, entries 2, 5, 12, 15, 20, and 21). However the *O*-arylation of 4'-hydroxyacetophenone and 4-cyanophenol with bromobenzene gave a very low yield (Table 4, entries 9 and 10), this might be due to the decreased nucleophilicity of phenols induced by the keto group and nitrile grouping. The *O*-arylation of 4-chlorophenol and aryl bromides gave good product yields (55–80%) (Table 4, entries 1, 11 and 19), which might be because substituent group (–Cl) only possess a weak electron-withdrawing ability. The coupling of 1 or 2-naphthol and aryl bromides (or 4-bromotoluene) was found to proceed in good yields (Table 4, entries 6, 7, 16 and 17). The results also indicated that the steric hindrance in both aryl

Table 4. Cu-Catalyzed Coupling Reaction of Aryl Bromide with Phenols^a

$\text{Ar}_1\text{-Br} + \text{Ar}_2\text{-OH} \xrightarrow[\text{CH}_3\text{CN, 81 } ^\circ\text{C, 24 h}]{\text{CuCl, L}_2} \text{Ar}_1\text{-O-Ar}_2$				
Entry	Ar ₁	Ar ₂	Product	Yield ^b (%)
1	1a	2a	3aa	78
2	1a	2c	3ac	73
3	1a	2e	3ae	67
4	1a	2f	3af	85
5	1a	2b	3ab	89
6	1a	2g	3ag	66
7	1a	2h	3ah	68
8	1a	2i	3ai	51
9	1a	2j	3aj	15
10	1a	2k	3ak	19
11	1b	2a	3ba	80
12	1b	2c	3bc	85
13	1b	2f	3bf	71
14	1b	2e	3be	59
15	1b	2b	3bb	84
16	1b	2g	3bg	61
17	1b	2h	3bh	74
18	1b	2d	3bd	75
19	1c	2a	3ca	55
20	1c	2c	3cc	61
21	1c	2b	3cb	66
22	1c	2e	3ce	41
23	1c	2d	3cd	79
24	1f	2c	3fc	95
25	1f	2b	3fb	95
26	1f	2e	3fe	72
27	1f	2a	3fa	86
28	1f	2d	3fd	91
29	1f	2k	3fk	56

^aUnless otherwise stated, General reaction conditions: 1.5 mmol of phenol, 1.0 mmol of ArBr, 2.0 mmol of K₃PO₄, 0.5 mL of anhydrous CH₃CN under Ar atmosphere for 24 h. ^bIsolated yield.

bromides and phenols had a influence on the coupling reaction (Table 4, entries 3, 4, 8, 13, 14, 26 and 19-23). For instance, the *O*-arylation of various substituted phenols and 2-bromotoluene gave only moderate to good product yields (41-79 %) (Table 4, entries 19-23), and only 51% yield was obtained after 24 h under our standard reaction conditions when 2, 6-dimethylphenol coupled with iodobenzene (Table 4, entry 8).

In summary, an efficient Cu-catalyzed synthesis of diaryl ethers from various aromatic iodides (bromides) and phenols was developed by using L₂(2-((*o*-toluidino)methyl)phenol)

as the ligand. The present protocol is applicable to a variety of phenols and aryl iodides (bromides) containing electron-withdrawing, electron-donating, and sterically demanding substrate combinations under mild conditions. The further study on design and application of new ligands in copper based Ullmann-type coupling reaction is currently ongoing.

Experimental

All the reactions were carried out in reaction tube under argon atmosphere. Reaction temperatures were controlled by temperature modulator; Thin-layer chromatography (TLC) was performed using silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence lamp. ¹H NMR and ¹³C NMR spectra were recorded on a 400 MHz instrument. Spectra were reported relative to Me₄Si (δ 0.0 ppm) or residual CDCl₃ (δ 7.26 ppm). ¹³C NMR were reported relative to CHCl₃ (δ 77.16 ppm). Low resolution mass spectra (LRMS) were recorded on mass spectrometer.

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