



Glyoxal bis(phenylhydrazone) as promoter for CuI-catalyzed O-arylation of phenols with bromoarenes

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ABSTRACT

A very simple bishydrazone-type ligand, glyoxal bis(phenylhydrazone) (**L1**), was found to effectively promote the CuI-catalyzed O-arylation of phenols with aryl bromides. This cross-coupling reaction proceeded in acetonitrile at 60–80 °C in the presence of K₃PO₄ as base. A diverse array of phenols and bromoarenes was employed as substrates to afford diaryl ethers in good to excellent yields, and some base-sensitive groups, such as ester, aldehyde, and ketone groups, can survive under the mild reaction conditions.

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Aryl ethers are an important class of ‘building blocks’ that are widely employed in organic synthesis, materials science, and pharmaceutical or agrochemical areas. The Cu-catalyzed Ullmann-type coupling reaction between aryl halides and phenols is recognized as a convenient and economic method for rapid access to diarylethers.¹ Major breakthroughs in the Ullmann condensations stemmed mainly from the introduction of organic additives into the reactions to form copper/ligand catalyst systems. Although ligand-free reaction conditions were utilized over a long period of time¹ and the study has been continued recently,² the use of ligands has proven to be significantly advantageous in improving the conditions, yields, and generality of reactions of this type. Representative ligands for copper-catalyzed diarylether synthesis included triphenylphosphine,³ neocuproine,⁴ *N,N*-dimethyl glycine,^{5,6} 2,2,6,6-tetramethylheptane-3,5-dione,⁷ nitrogen-based multidentate ligands,⁸ and pyrrolidine-2-phosphonic acid monoester.⁹ Despite these remarkable advances, we found that most of the reactions were carried out at reaction temperatures of 100–110 °C, and there were only few examples that occurred at less than 100 °C.^{5,6} Hence, search for new, more active ligands remains to be of value and interest for Cu-catalyzed aromatic C–O couplings.

By considering the importance of steric/electronic natures and coordination diversity in the molecular design of ligands, we were strongly interested in glyoxal bishydrazones as potential ligands because (1) they are readily available from the condensation of glyoxal with hydrazines, and conveniently manipulated due to insensitivity to air/moisture; (2) they possess coordination versatility stemming from multifold σ - and π -donating properties as well as a flexible molecular backbone; and (3) their steric and electronic

effects may be easily tuned by changing the groups on the hydrazine or aldehyde section. While the use of bishydrazone-type frameworks as ligands has been seen in palladium catalyses,^{10,11} its utility in copper-catalyzed processes has not yet been demonstrated. Herein, we want to present our study on the application of glyoxal bishydrazone-type ligands to the copper-catalyzed diarylether synthesis.

Two glyoxal bishydrazones (**L1** and **L2**) and, for comparison, two monohydrazones with the chelating property (**L3** and **L4**) were chosen and examined (Fig. 1). Initially, a systematic screening of reaction conditions was performed using CuI/**L1** as catalytic system in a model reaction of phenol and bromobenzene (Table 1). First, we found that the nature of reaction solvents seems to be very important for this reaction. In dioxane, a high yield of 90% could be obtained at 100 °C in the presence of K₃PO₄ as base (Table 1, entry 1); stronger bases (Cs₂CO₃ and *t*-BuOK) are less efficient as compared to weak bases (K₃PO₄ and K₂CO₃) (entries 1 and 2 vs entries 3 and 4). Toluene (entry 5) or THF (entries 6 and 7) as the reaction solvent gave a low yield of or no product under the similar conditions. To our pleasure, acetonitrile was found to be

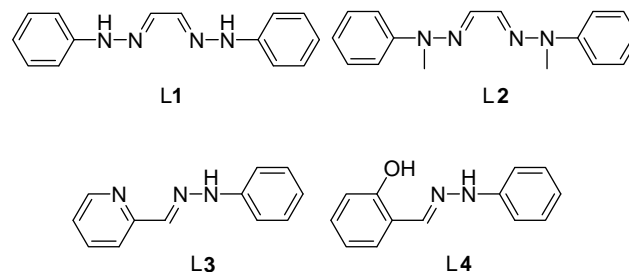
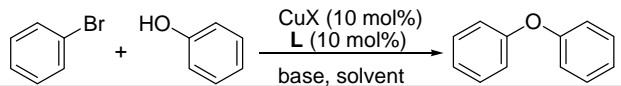


Figure 1. Hydrazone-type ligands used in this study.

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Table 1
Screening of reaction conditions for the Cu(I)-catalyzed coupling of phenol and bromobenzene^a



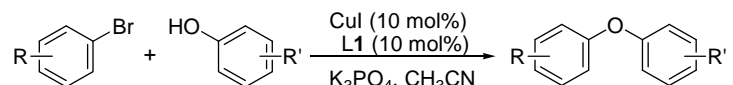
Entry	Ligand	Catalyst	Base	Solvent	Temperature (°C)	Isolated yield (%)
1	L1	CuI	K ₃ PO ₄	Dioxane	100	90
2	L1	CuI	K ₂ CO ₃	Dioxane	100	36
3	L1	CuI	Cs ₂ CO ₃	Dioxane	100	12
4	L1	CuI	KOBu ^t	Dioxane	100	10
5	L1	CuI	K ₃ PO ₄	Toluene	100	49
6	L1	CuI	K ₃ PO ₄	THF	70	None
7	L1	CuI	KOBu ^t	THF	70	None
8	L1	CuI	Cs ₂ CO ₃	CH ₃ CN	80	82
9	L1	CuI	K ₂ CO ₃	CH ₃ CN	80	80
10	L1	CuI	K ₃ PO ₄	CH ₃ CN	60	90
11	L1	CuBr	K ₃ PO ₄	CH ₃ CN	80	60
12	L1	CuCl	K ₃ PO ₄	CH ₃ CN	80	56
13	L2	CuI	K ₃ PO ₄	CH ₃ CN	80	57
14	L2	CuI	K ₃ PO ₄	Dioxane	100	37
15	L3	CuI	K ₃ PO ₄	CH ₃ CN	80	90
16	L4	CuI	K ₃ PO ₄	CH ₃ CN	80	37
17	None	CuI	K ₃ PO ₄	CH ₃ CN	80	None

^a Reaction conditions: bromobenzene (1.5 mmol), phenol (1 mmol), Cu(I) salt (10 mol %), ligand (10 mol %), base (2 mmol), solvent (1 mL), 12 h.

an excellent solvent in which the coupling reaction always gave appreciable yields whether strong or weak bases are used (entries 8–10). An excellent yield of 90% was achieved by performing the reaction with CuI–L1 catalyst system in acetonitrile at 60 °C in the presence of K₃PO₄ as base (entry 10). Subsequently, we investigated effects of copper(I) sources and other ligands on this reaction. It was found that the activity of cuprous halide in the reaction decreased in the order of CuI > CuBr > CuCl (entries 10–12). To our surprise, glyoxal bis(1-methyl-1-phenylhydrazone) (L2), the N,N-dimethylated derivative of L1, gave a dramatically reduced yield of 57% (entry 13). An attempt to elevate reaction temperatures could not offer a good outcome, either (entry 14), indicating that the proper choice of ligands plays a fundamental role in the reaction. Further, two monohydrazone-type ligands, 2-pyridinecarboxaldehyde phenylhydrazone (L3) and salicylal phenylhydrazone (L4), were surveyed. As a result, L3 could work well if the reaction temperature is elevated from 60 °C to 80 °C (entry 15), while L4 was far inferior to L1 (entry 16). Then, the role of L1 in the reaction was demonstrated by a control reaction without the use of ligands (entry 17), where no diphenylether was formed. Finally, we set up the optimized reaction conditions as entry 10 in Table 1.

Under the optimized conditions, the coupling reaction between a range of phenols and aryl bromides was investigated to know about the scope of our method (Table 2). For phenols, electron-neutral (Table 2, entries 1, 4–6, 19, and 20) and –rich ones (Table

Table 2
O-Arylation of phenols with aryl bromides catalyzed by CuI/L1 system^a



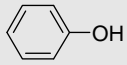
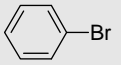
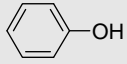
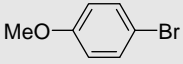
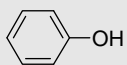
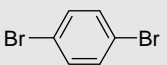
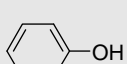
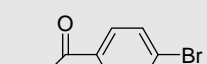
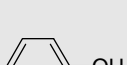

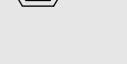
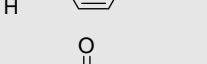
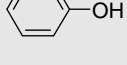
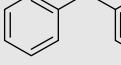
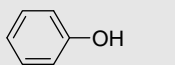
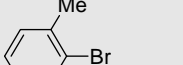
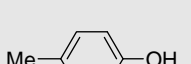
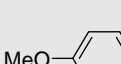
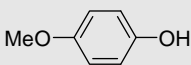
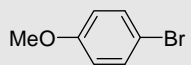
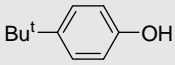
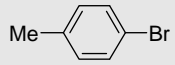
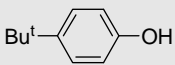
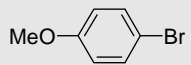
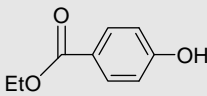
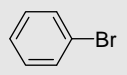
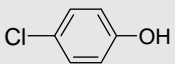
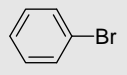
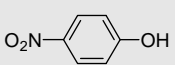
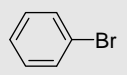
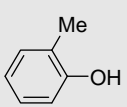
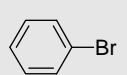
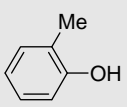
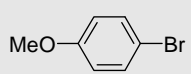
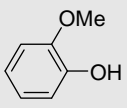
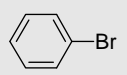
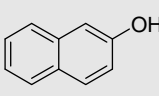
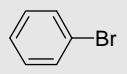
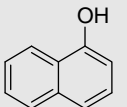
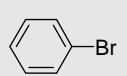
Entry	Phenol	Aryl halide	Temperature (°C)	Isolated yield (%)
1			60	90
2			80	75
3			80	60 ^b
4			60	80
5			60	92
6			60	80
7			80	60
8			80	75
9			60	92

Table 2 (continued)

Entry	Phenol	Aryl halide	Temperature (°C)	Isolated yield (%)
10			80	75
11			80	80
12			80	65
13			80	65
14			80	80
15			60	0
16			60	80
17			80	70
18			60	80
19			60	78
20			60	75

^a Reaction conditions: aryl bromide (1.5 mmol), phenol (1 mmol), CuI (10 mol %), L1 (10 mol %), K₃PO₄ (2 mmol), CH₃CN (1 mL), 60 °C, 12 h.

^b Dibromide (1 mmol), phenol (4 mmol). The double-etherified product, 4-phenoxydiphenylether, was afforded.

2, entries 10, 11, 16, and 18) were viable substrates, and offered the desired products in good to excellent yields. The tolerance of base-sensitive groups on the phenol was observed (entry 13). On the other hand, phenols bearing weak electron-withdrawing group reacted smoothly (entries 13 and 14), while those bearing strong electron-withdrawing groups seemed difficult to undergo the O-arylation desired. For example, 4-nitrophenol (entry 15) and 4-formalphenol (unlisted in Table 2) did not react at all, and the phenols were recovered. It is noteworthy that the steric hindrance of phenols would not exert a significant effect on this reaction since the reaction of 2-methyl and 2-methoxy phenols (entries 16–18), and 1-naphthol (entry 20) with some aryl bromides could give reasonable yields. This might be because the *ortho*-substituent on the phenol, compared to that on the bromide (see below), is a little farther away from copper center in the intermediate complex formed in the catalytic cycle steps, and hence would produce a smaller hindrance to formation of the complex.

As for bromoarenes, electron-neutral (Table 2, entries 1, 9, 16, and 18–20) and -deficient (entries 4–6) ones were good substrates for this reaction, providing the desired diaryl ethers in good to excellent yields. But the reaction of electron-rich bromoarenes (entries 2, 8, 10–12, and 17) was slightly difficult, and needed a higher reaction temperature of 80 °C to offer the desired products with good yields. On the other hand, the reaction was very sensitive to the steric effects of aryl bromides (entry 7). This reason might be attributed to what has been described above (see above). Alike, base-sensitive groups on the aryl bromide, such as ester (entry 4), aldehyde (entry 5), and non-enolized ketone (entry 6), can be tolerated under the reaction conditions. In addition, dibromobenzene can undergo a double-coupling reaction with a moderate yield when enough amounts of phenol are used (entry 3).

By surveying several selected cases, we found that the change in the relative molar ratio between bromoarene and phenol did not produce an essential effect on yields of the reaction. Based on

our own observation, a major side-reaction in the reaction might be debromination of aryl bromides (i.e., the reduction of aryl bromides to the corresponding arene). Additionally, in some cases, particularly for electron-rich bromoarene substrates, the self-coupling to produce diaryls was a detectable side-reaction.

In summary, a simple and efficient CuI/glyoxal bis(phenylhydrazone) catalytic system has been developed for the aromatic C–O coupling reaction. Under mild reaction conditions, diarylether could be obtained in good to excellent yields from cheaper starting materials, inexpensive reagents and easily handled reaction solvents. This protocol provides a useful alternative and complement to the corresponding copper and palladium processes for diarylether synthesis.

General procedure for the CuI-catalyzed O-arylation of phenols with aryl bromides: Under N₂ atmosphere, a 100-mL three-necked flask was charged with phenol (1 mmol), potassium phosphate (2 mmol), hydrazone ligand L1 (10 mol % with respect to phenol), CuI (10 mol % with respect to phenol), aryl bromide (1.5 mmol), and the dried CH₃CN (1 mL). Care was taken to make sure the contents were well stirred. The reaction mixture was then heated in an oil bath of 60 or 80 °C during times that are indicated in Table 2. The reaction mixture was cooled to room temperature, mixed with 15 mL of diethyl ether, and filtered to remove any insoluble residues. Solvents were removed under reduced pressure, and the residue purified by column chromatography on silica gel (60–90 °C petroleum ether) to obtain the analytically pure product in the isolated yields indicated in Table 2. All diarylether products in this Letter are known compounds, and are partly characterized by ¹H

NMR and MS, and compared to authentic samples or the literature data.

Acknowledgments

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