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An efficient BINAM–copper(II) catalyzed Ullmann-type synthesis of diaryl ethers

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Abstract

A wide range of diaryl ethers are synthesized from the corresponding aryl iodides and phenols through Ullmann type coupling reactions in the presence of a catalytic amount of easily available BINAM–Cu$(OTf)_2$ complex under mild reaction conditions. Less reactive aryl bromides have also been shown to react with phenols under identical reaction conditions to give good yields of the diaryl ethers without increasing the reaction temperature and time.

Keywords: Copper catalyst; Coupling reaction; Diaryl ether; Diamine ligands; Ullmann coupling

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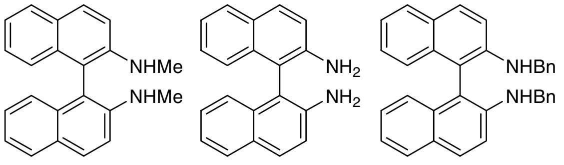
Diaryl ethers constitute a very important class of organic compounds playing a significant role in a number of chemical and pharmaceutical industries.[1] A number of them have been shown to possess significant biological activity[2] and the diaryl ether structural unit is prevalent in numerous weed-killing chemicals.[3] Palladium catalyzed diaryl ether formation from the corresponding aryl halide and phenol or its sodium salt used to be the method of choice.[4] However, the high costs of palladium salts, high oxophillicity associated with phosphine ligands, and tedious multistep processes involved in the synthesis of these ligands have rendered Pd unpopular, particularly for large scale reactions.[5]



1 **2** **3**

Use of stoichiometric copper as demonstrated by Ullmann in 1904[6] itself, requires drastic conditions. In fact, only in the last few years have the considerable efforts taken to improve the efficiency of this reaction started to bear fruit with the use of copper salts with several ligands such as 1-naphthoic acid,[7] 1,10-phenanthroline,[8] neocuproine,[9] triphenylphosphine,[10] 2,2,6,6-tetramethylheptane-3,5-dione,[11] tripod ligands,[12] diimine ligands,[13] β-keto ester,[14] tetraethyl orthosilicate (as solvent),[15] silica supported Cu(II),[16] and aryl boronic acid.[17]

It is thought that these ligands increase the efficiency of the Ullmann reaction by increasing the solubility of the copper salts by preventing their aggregation. However, this advance in the field of Ullmann coupling is not sufficient as most of the reactions still require long reaction times (more than 24 h), high reaction temperatures (120–220 °C) and in some cases, high catalytic loading (even super stoichiometric amounts of ligands are needed). Therefore a mild, economic, and efficient catalytic system is still desirable for this process.

We have developed efficient methodologies for the selective oxidation of alcohols to the corresponding carbonyl compounds and carboxylic acids using Cu catalysts.[18] As a part of our ongoing research toward copper catalyzed

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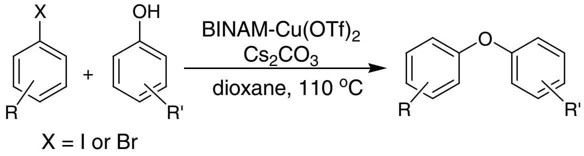


Scheme 1.

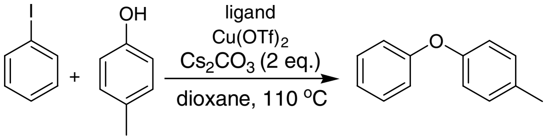
organic transformations, herein, for the first time we report an easily available 1,1′-binaphthyl-2,2′-diamine (BINAM)–copper(II) complex catalyzed Ullmann coupling for the formation of diaryl ethers through C–O bond formation in dioxane under mild conditions (Scheme 1). This procedure is very simple, mild, clean, and works efficiently without any additives.

In preliminary studies, we used 20 mol % *N*,*N*′-dimethyl-1,1′-binaphthyl-2,2′-diamine **1** (*N*,*N*′-dimethyl-BINAM) ligand with 20 mol % of $Cu(OTf)_2$ for the coupling of iodobenzene with *p*-cresol in dioxane at 110 °C. Iodobenzene was fully consumed in 15 h and the reaction provided a 68% isolated yield of the corresponding diaryl ether (Table 1, entry 1).

When the ligand *N*,*N*′-dimethyl BINAM **1** was replaced with BINAM **2**, surprisingly the reaction provided an 80% yield of the diaryl ether. However, replacing BINAM **2** by ligand **3** reduced the yield to 69%. Next, the reaction was carried out with different ratios of BINAM and $Cu(OTf)_2$ and it was found that 20 mol % of ligand–copper combination was the most effective catalytic system.

The reaction was screened with several copper salts, solvents, and bases to increase the efficiency of the coupling reactions and the results are summarized in Table 2. Although several copper salts catalyzed the reaction, $Cu(OTf)_2$ turned out to be the copper salt of choice in view of reaction time and yield (Table 2, entry 1). Similarly, dioxane was the best solvent among those examined. Cs_2CO_3 as base gave the best yields of product in comparison with bases such as Na_2CO_3 and K_2CO_3.

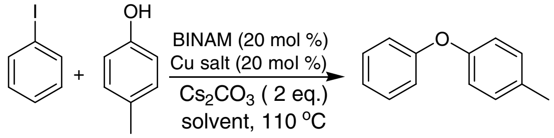
Table 1
Effect of the ratio of ligand and $Cu(OTf)_2$



Entry	Ligand (mol %)	$Cu(OTf)_2$ (mol %)	Time (h)	Yield[a] (%)
1	**1** (20)	20	15	68
2	**2** (20)	20	18	80
3	**3** (20)	20	18	69
4	**2** (5)	20	25	40
5	**2** (10)	20	20	65
6	**2** (10)	10	24	51
7	**2** (15)	15	24	66

[a] Isolated yield.

Table 2
Effect of Cu salts, solvents, and base



Entry	Cu salt	Solvent	Time (h)	Yield[a] (%)
1	$Cu(OTf)_2$	Dioxane	18	80
2	CuI	Dioxane	22	71
3	CuBr	Dioxane	22	76
4	$CuCl_2$	Dioxane	24	50
5	CuCl	Dioxane	24	55
6	$Cu(OAc)_2$	Dioxane	30	55
7	$Cu(OTf)_2$	THF	26	27[b]
8	$Cu(OTf)_2$	Toluene	20	59
9	$Cu(OTf)_2$	MeCN	24	40[b]
10	$Cu(OTf)_2$	DMSO	22	56
11	$Cu(OTf)_2$	Xylene	24	35
12	$Cu(OTf)_2$	Dioxane	26	0[c]
13	$Cu(OTf)_2$	Dioxane	26	40[d]

[a] Isolated yield.

[b] Reaction was carried out in a pressure tube.

[c] Na_2CO_3 was used as base instead of Cs_2CO_3.

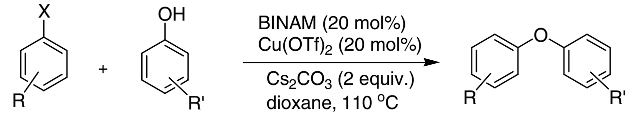
[d] K_2CO_3 was used as base instead of Cs_2CO_3.

Using the above mentioned optimized conditions, we initiated our investigations into the scope of the BINAM–$Cu(OTf)_2$ catalyzed Ullmann type coupling and the results are summarized in Table 3. Various aryl iodides and phenols reacted to give the corresponding diaryl ethers. We found that iodobenzene reacted with phenols containing electron-releasing groups as well as electron-withdrawing groups. Also, even in the presence of an *ortho* substituted phenol (which is capable of providing scope for steric bias) the reaction proceeded smoothly. However, the yields were different with electron rich and electron deficient phenols. Electron-releasing groups such as methyl and methoxy phenol increased the yield of the diaryl ether (entries 2 vs 1, 3 and 5), whereas an electron-withdrawing group such as chloride in the phenolic moiety decreased the yield of the product (entries 2 vs 7).

In the aryl iodide component, the presence of a methoxy group at the *para* position decreased the yield of the coupling reaction by about 5–10% (entries 8–11 vs 1, 2, 4 and 6). Similarly, the presence of an *o*-methoxy group in iodobenzene further decreased the yield by 5% to give a 65% isolated yield of the diaryl ether (entry 12). The yield in this coupling reaction was increased when the electron-releasing methoxy group was present at the *meta* position in iodobenzene. We achieved a 90% isolated yield of the corresponding diaryl ether when we coupled *m*-methoxyiodobenzene with *m*-methoxyphenol (entry 15).

We were pleased to note that under our optimized reaction conditions, aryl bromides also reacted with phenols to provide the corresponding diaryl ethers. 1-Bromo-4-methylbenzene and 1-bromo-4-methoxybenzene reacted with methyl-substituted phenols to give the corresponding diaryl

Table 3
Coupling reaction of aryl halides with phenols in the presence of BINAM–Cu(OTf)$_2$ catalyst



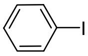
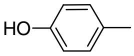
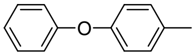
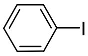
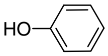
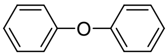
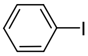
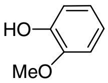
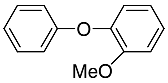
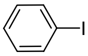
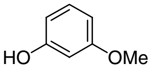
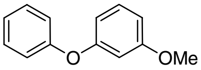
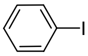
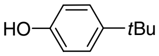
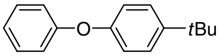
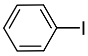
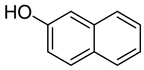
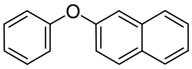
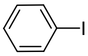
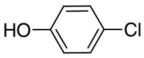
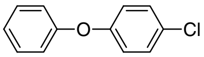
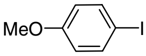
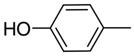
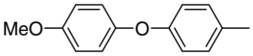
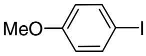
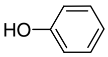
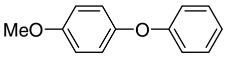
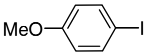
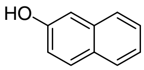
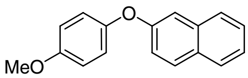
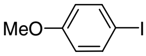
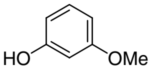
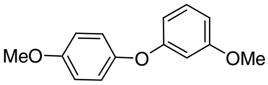
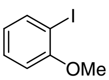
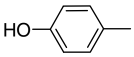
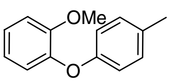
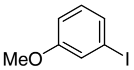
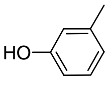
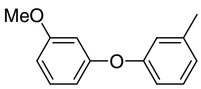
Entry	Aryl halide	Phenol	Time (h)	Product[a]	Yield[b] (%)
1			18		80
2			18		70
3			19		75
4			16		84
5			15		72
6			22		66
7			15		60
8			14		70
9			14		62
10			28		60
11			36		75
12			10		65
13			22		72

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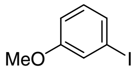
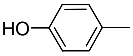
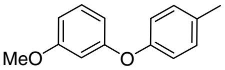
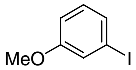
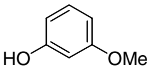
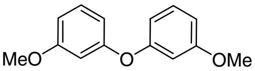
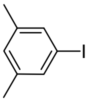
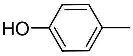
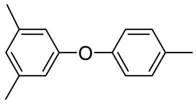
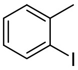
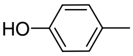
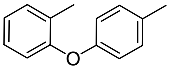
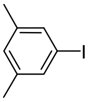
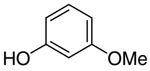
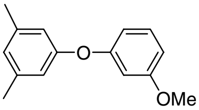
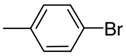
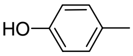
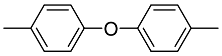
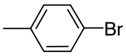
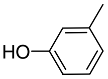
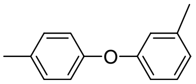
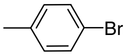
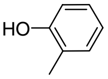
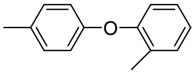
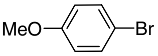
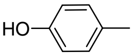
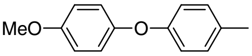
Table 3 (*continued*)

Entry	Aryl halide	Phenol	Time (h)	Product[a]	Yield[b] (%)
14			18		80
15			20		90
16			24		64
17			20		75
18			18		70
19			22		62
20			20		60
21			18		76
22			28		66

[a] All the diaryl ethers gave satisfactory spectral data.

[b] Isolated yield.[19]

ethers in good isolated yields. It is very important to mention that in general, aryl bromides are less reactive than aryl iodides and require much more drastic reaction conditions for arylation. However in the presence of our BINAM–Cu(OTf)$_2$ catalyst even aryl bromides reacted with phenols to give good yields of the expected diaryl ethers without increasing the reaction temperature and time.

In summary, we have developed an efficient, experimentally simple, and economically attractive copper catalyzed O-arylation of phenols with aryl iodides. Aryl bromides can also be used for O-arylation of phenols under the same reaction conditions without increasing the reaction temperature. The presence of an electron-releasing group such as methoxy at the *ortho* and *para* positions of phenol decreased the yield of the coupling reaction whereas the presence of a methoxy group at the *meta* position increased the yield of the coupling reaction. Efforts to expand the utility of our new catalytic system to other classes of nucleophiles will be reported in due course.

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19. *Typical representative experimental procedure*: Cs_2CO_3 (325.8 mg, 1 mmol), $Cu(OTf)_2$ (36.1 mg, 0.1 mmol), and BINAM (28.4 mg, 0.1 mmol) were taken in a 25 mL two neck round bottom flask capped with a septum. The flask was evacuated and back-filled with nitrogen three times. Dioxane (5 mL) was added to the reaction mixture at room temperature. To the resulting brown colored solution was added iodobenzene (55.9 μL, 0.5 mmol) followed by *p*-cresol (62.7 μL, 0.6 mmol). The septum was replaced with a glass stopper and the reaction mixture was heated for 18 h at 110 °C (the progress of the reaction was followed by TLC). After complete disappearance of iodobenzene (TLC), the reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The crude residue was purified by column chromatography on silica gel using ethyl acetate/hexane as the eluent to afford 1-phenoxy-4-methylbenzene (73.6 mg, 80%) as a colorless oil; R_f 0.73 (in hexanes); FTIR (neat) 1233, 2922, 3029 cm^{-1}; ^1H NMR(400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 6.91 (d, $J = 7.6$ Hz, 2H), 6.97 (d, $J = 8.4$ Hz, 2H), 7.05 (t, $J = 7.4$ Hz, 1H), 7.12 (d, $J = 8.4$ Hz, 2H), 7.29 (t, $J = 8.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 118.3, 119.1, 122.8, 129.6, 130.2, 132.8, 154.7, 157.8.[20]
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