

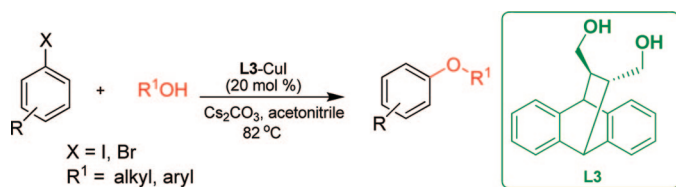
General, Mild, and Intermolecular Ullmann-Type Synthesis of Diaryl and Alkyl Aryl Ethers Catalyzed by Diol–Copper(I) Complex[†]

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A wide range of diaryl ethers and alkyl aryl ethers are synthesized through intermolecular C(aryl)–O bond formation from the corresponding aryl iodides/aryl bromides and phenols/alcohols through Ullmann-type coupling reaction in the presence of a catalytic amount of easily available (\pm)-diol **L3**-CuI complex under very mild reaction conditions. Less reactive aryl bromides can also be used for *O*-arylation of phenols under the same reaction conditions without increasing the reaction temperature, catalyst loading, and time. The catalytic system not only is capable of coupling hindered substrate but also tolerates a broad range of a series of functional groups.

1. Introduction

Numerous synthetically challenging and medicinally important chemicals contain diaryl ethers and alkyl aryl ethers as structural units.^{1,2} Palladium-catalyzed diaryl ether and alkyl aryl ether formation from the corresponding aryl halide and phenol/alcohols or its sodium salt used to be the method of choice.³ However, the high costs of palladium salts, high oxophilicity associated with phosphine ligands, and tedious

multistep processes involved in the synthesis of these ligands have rendered Pd unpopular, particularly for large scale reactions.⁴ Copper-catalyzed Ullmann coupling between an aryl halide and phenol/alcohols is an alternate for palladium catalyzed diaryl ether/alkyl aryl ether synthesis. However, harsh reaction conditions such as high temperatures (120–220 °C), the usual requirement of stoichiometric quantities of copper catalysts, and low to moderate yields have generally limited the utility of copper catalyst.⁵ In fact, only in the past 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,⁶ 1,10-phenanthroline,⁷ neocuproine,⁸ triphenylphosphine,⁹ 2,2,6,6-tetramethylheptane-

[†] This paper is dedicated to Prof. Veejendra K. Yadav.

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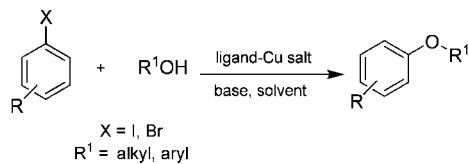
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SCHEME 1



3,5-dione,¹⁰ tripod ligands,¹¹ tetraethyl orthosilicate (as solvent),¹² silica supported Cu(II) complex,¹³ aryl boronic acid,¹⁴ *N,N*-dimethylglycine,¹⁵ diimine ligands,¹⁶ β -keto ester,¹⁷ and bipyridyl complex.¹⁸ Very recently diketone along with iron^{19,20} has also been used as efficient catalyst for the formation of C(aryl)-O bond.

Recently we have shown that 1,1'-binaphthyl-2,2'-diamine (BINAM)-Cu(OTf)₂ complex can be used as an efficient catalyst for diaryl ether and alkyl aryl ether synthesis through C–O bond formation in dioxane from aryl iodides and phenols/alcohols at 110 °C.²¹ As a part of our ongoing research toward finding more efficient copper catalyst for diaryl ether and alkyl aryl ethers synthesis from aryl halides and phenols/alcohols, herein for the first time we report an easily available racemic anthracene-based diol, *trans*-9,10-dihydro-9,10-ethanoanthracene-11,12-dimethanol²² **L3**-CuI complex, as an efficient catalyst for Ullmann coupling for the formation of diaryl and alkyl aryl ethers through C–O bond formation in acetonitrile under very mild conditions (82 °C). This procedure is very simple, mild, clean and works efficiently (Scheme 1).

2. Results and Discussion

In preliminary studies, we used 20 mol % 1,1'-binaphthyl-2,2'-diol **L1** (BINOL) (Figure 1) as ligand with 20 mol % CuI for the coupling of iodobenzene with *p*-cresol in acetonitrile at 82 °C. After 28 h the coupling reaction provided 55% yield for the corresponding diaryl ether (Table 1, entry 1). When the BINOL **L1** was replaced by diester ligand **L2**, the reaction provided only 49% yield of diaryl ether. Surprisingly, when diol **L3** was used as ligand along with CuI, it provided 97% yield (entry 3). However, replacing **L3** by **L4**, the reaction failed to provide any coupling product (entry 4), and using (+)-diethyl tartarate **L5** as ligand gave only 45% yield for corresponding diaryl ether (entry 5). The C(aryl)–O bond formation between iodobenzene and *p*-cresol in the presence of 20 mol % *N,N*-dimethylglycine **L6**-CuI gave only 55% yield in acetonitrile at 82 °C (entry 8). Changing the solvent to dioxane increased the

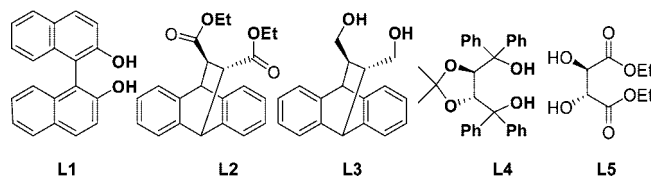


FIGURE 1. Oxygen-based ligands for copper-catalyzed C–O bond formation.

TABLE 1. Effect of the Ratio of Ligand and CuI

| entry | ligand | CuI | time (h) | yield (%) |
|-------|----------------|----------|----------|-----------------|
| 1 | L1 (20 mol %) | 20 mol % | 28 | 55 |
| 2 | L2 (20 mol %) | 20 mol % | 28 | 49 |
| 3 | L3 (20 mol %) | 20 mol % | 17 | 97 |
| 4 | L4 (20 mol %) | 20 mol % | 30 | 00 |
| 5 | L5 (20 mol %) | 20 mol % | 30 | 45 |
| 6 | L3 (10 mol %) | 10 mol % | 24 | 76 |
| 7 | L3 (20 mol %) | 10 mol % | 24 | 33 |
| 8 | L6 (20 mol %) | 20 mol % | 16 | 55 |
| 9 | L6 (20 mol %) | 20 mol % | 17 | 80 ^a |
| 10 | L6 (7.5 mol %) | 2 mol % | 18 | 75 ^a |
| 11 | L6 (7.5 mol %) | 2 mol % | 18 | 42 |
| 12 | – | – | 32 | 00 |
| 13 | – | 20 mol % | 32 | 39 |

^a Dioxane was used as solvent.

yield to 80% (entry 9). Then the reaction was carried out with different ratios of **L3** and CuI, and it was found that a 20 mol % ligand **L3**-copper combination was the most effective catalytic system. The coupling reaction did not provide even a trace amount of diaryl ether when the reaction was carried out without **L3**-CuI (entry 12). When the reaction was carried out only with CuI without **L3**, the reaction provided only 39% yield for the coupling product (entry 13), which shows that ligand is mandatory for quantitative yield of the product.

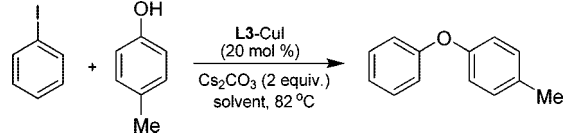
The reaction was screened with several copper salts, solvents, and bases to increase the efficiency of the coupling reactions, and the results are summarized in Table 2. Although several copper salts catalyzed the reaction, CuI turned out to be the copper salt of choice in view of yield (Table 2, entry 1). Similarly acetonitrile was the best solvent among those examined. Cs₂CO₃ as base gave the best yields of product in comparison with bases such as Na₂CO₃ and K₂CO₃.

Using the above-mentioned optimized conditions, we initiated our investigations into the scope of the **L3**-CuI catalyzed Ullmann-type coupling reaction, and the results are summarized in Table 3. Various aryl iodides and phenols reacted to give the corresponding diaryl ethers under very mild reaction conditions. We found that iodobenzene containing electron-releasing groups as well as electron-withdrawing groups reacted with phenols to give corresponding diaryl ethers.

The yields were different with electron-rich and electron-deficient phenols. The presence of electron-releasing groups such as methyl and methoxy groups in phenol at *para* and *meta* positions increased the yield of the diaryl ethers by 5–23% (entries 2 vs 1, 4, 5, and 8), whereas an electron-withdrawing group such as a chloro group at the *para* position of phenol decreased the yield to 64% yield (entries 1 vs 10). The presence of an electron-releasing group such as a methoxy or methyl

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 (22) Diol ligand **L3** was easily synthesized from known literature procedure. See Supporting Information for experimental details.

TABLE 2. Effect of Cu Salts, Solvents, and Bases



| entry | Cu salt | solvent | time (h) | yield (%) |
|-------|----------------------|---------------|----------|-----------------|
| 1 | CuI | acetonitrile | 17 | 97 |
| 2 | Cu(OTf) ₂ | acetonitrile | 15 | 63 |
| 3 | CuBr | acetonitrile | 14 | 73 |
| 4 | CuCl ₂ | acetonitrile | 18 | 49 |
| 5 | CuCl | acetonitrile | 16 | 67 |
| 6 | Cu(OAc) ₂ | acetonitrile | 20 | 52 |
| 7 | CuSO ₄ | acetonitrile | 14 | 68 |
| 8 | CuI | toluene | 24 | 52 ^a |
| 9 | CuI | DMF | 18 | 32 ^a |
| 10 | CuI | DMSO | 20 | 45 ^a |
| 11 | CuI | xylylene | 30 | 15 ^a |
| 12 | CuI | dioxane | 17 | 90 ^a |
| 13 | CuI | chlorobenzene | 36 | 5 ^a |
| 14 | CuI | acetonitrile | 30 | 0 ^b |
| 15 | CuI | acetonitrile | 30 | 38 ^c |

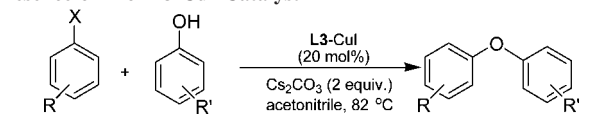
^a Reaction was carried out at 110 °C. ^b Na₂CO₃ was used as base. ^c K₂CO₃ was used as base.

group in iodobenzene moiety at the *para* position decreased the yield of the product by 4–22% (entries 1 vs 11 and 2 vs 12).

As expected, the presence of electron-withdrawing groups in aryl iodide moiety drastically increased the yield as well as the reaction rate for the coupling reaction with phenols for C–O bond-formation reaction. When a very strong electron-withdrawing group such as a nitro group is present at the *para* position of iodobenzene, the reaction proceeded even without L3-CuI complex, showing that the iodide is activated and the reaction is taking place through a nucleophilic addition elimination mechanism rather than a copper complex catalyzed coupling reaction (entry 20). To our surprise when the same electron-withdrawing nitro group is present at the *meta* position of the iodobenzene, the reaction did not provide even a trace amount of the corresponding diaryl ether without L3-CuI complex, and the same reaction provided 85% of yield of the corresponding diaryl ethers in the presence of our L3-CuI in acetonitrile at 82 °C (entry 19). Also, even in the presence of an *ortho*-substituted phenol (which is capable of providing scope for steric bias), the reaction proceeded smoothly to give the diaryl ethers in good yields (entries 3, 7, and 9). The highest yield that is quantitative yield was obtained when *m*-methoxy iodobenzene was reacted with *p*-cresol (entry 16). This clearly shows that the presence of an electron-donating methoxy group at the *meta* position of iodobenzene increases the efficiency of the reaction, whereas the presence of a methoxy group at the *para* position of iodobenzene decreases the yield of the coupling reaction drastically (entries 11–14 vs 15 and 16).

We were pleased to note that under our optimized reaction conditions, aryl bromides also reacted with phenols without increasing catalyst loading and reaction temperature to provide the corresponding diaryl ethers in good yields (Table 4). Both electron-releasing and electron-withdrawing groups containing aryl bromides, such as 1-bromo-4-methylbenzene, 1-bromo-4-methoxy benzene, 1-bromo-2-methoxy benzene, and 1-bromo-4-cyanobenzene, reacted with a variety of phenols to give the corresponding diaryl ethers in good yields. Even sterically hindered *ortho*-substituted aryl bromide reacted with phenol,

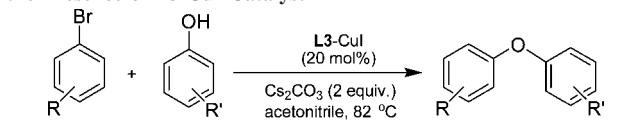
TABLE 3. Coupling Reaction of Aryl Iodide with Phenols in the Presence of Diol L3-CuI Catalyst



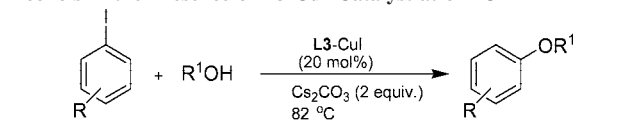
| Entry | aryl iodide | product | time (h) | yield (%) |
|-------|-------------|---------|----------|-----------------|
| 1 | | | 17 | 97 |
| 2 | | | 19 | 74 |
| 3 | | | 23 | 71 |
| 4 | | | 18 | 88 |
| 5 | | | 20 | 79 |
| 6 | | | 19 | 65 |
| 7 | | | 25 | 95 |
| 8 | | | 15 | 85 |
| 9 | | | 20 | 55 |
| 10 | | | 25 | 64 |
| 11 | | | 20 | 75 |
| 12 | | | 20 | 70 |
| 13 | | | 20 | 66 |
| 14 | | | 20 | 64 |
| 15 | | | 17 | 97 |
| 16 | | | 22 | 99 |
| 17 | | | 22 | 93 |
| 18 | | | 22 | 76 |
| 19 | | | 12 | 85 |
| 20 | | | 10 | 96 ^a |

^a Reaction takes place without diol 3-Cu complex.

and the reaction proceeded smoothly to give the diaryl ether in good yield (entry 10). Similarly, *ortho*-substituted phenol reacted with 1-bromo-4-methylbenzene to give the corresponding diaryl ether with 65% yield (entry 7). It is very important to mention that, in general, aryl bromides are less reactive than aryl iodides

TABLE 4. Ullmann Coupling of Aryl Bromides with Phenols in the Presence of L3-CuI Catalyst


| Entry | aryl bromide | product | time (h) | yield (%) |
|-------|--------------|---------|----------|-----------|
| 1 | | | 24 | 69 |
| 2 | | | 20 | 73 |
| 3 | | | 22 | 68 |
| 4 | | | 22 | 54 |
| 5 | | | 24 | 78 |
| 6 | | | 22 | 68 |
| 7 | | | 27 | 65 |
| 8 | | | 27 | 69 |
| 9 | | | 24 | 63 |
| 10 | | | 26 | 63 |
| 11 | | | 26 | 71 |
| 12 | | | 24 | 88 |

TABLE 5. Ullmann Coupling of Aryl Iodides with Aliphatic Alcohols in the Presence of L3-CuI Catalyst at 82 °C


| Entry | aryl iodide | product | time (h) | yield (%) |
|-------|-------------|---------|----------|-----------|
| 1 | | | 22 | 92 |
| 2 | | | 24 | 80 |
| 3 | | | 35 | 75 |
| 4 | | | 26 | 60 |
| 5 | | | 26 | 51 |
| 6 | | | 29 | 61 |
| 7 | | | 30 | 58 |
| 8 | | | 36 | 50 |
| 9 | | | 36 | 56 |
| 10 | | | 26 | 75 |

and require much more drastic reaction conditions for arylation. However, in the presence of diol ligand **3**-CuI catalyst even a variety of aryl bromides reacted with phenols to give good yields of the expected diaryl ethers through C–O bond formation without increasing the catalyst loading, reaction temperature, and time.

2.1. Coupling of Aryl Iodides with Aliphatic Alcohols.

After successful completion of diaryl ether formation at 82 °C from corresponding aryl halide and phenols in the presence of **L3**-CuI, we applied the same protocol for coupling of aryl iodides with aliphatic alcohols for the synthesis of alkyl aryl ethers at 82 °C (Table 5). It was found that primary alcohols such as methanol, ethanol, *n*-propanol, *n*-butanol, and allylic alcohol can be successfully coupled with various iodobenzenes with good yields. In the case of the aryl iodide component, the presence of both electron-releasing groups such as a methoxy group or electron-withdrawing group such as a nitro group were tolerated to give the corresponding alkyl aryl ethers in good yields. Moving the electron-releasing methoxy group in iodobenzene from the *para* position to the *meta* position decreased the yield of the coupling reaction (entries 1 vs 5). The presence of an *ortho* substitution in iodobenzene (which is capable of providing scope for steric bias) also provided the C–O bond-forming reactions smoothly to give 61% and 50% yields, respectively (entries 6 and 8).

The advantage of our catalytic system is that it provides the arylation of phenols and aliphatic alcohols at 82 °C, whereas

most of other copper-catalyzed reactions require higher temperature.^{6–14} It is very important to mention that arylation of phenols with less reactive aryl bromides also carried out without increasing the catalytic loading and reaction temperature. There are only very few reports in the literature for arylation of phenols at lower temperature. Ma *et al.* carried out the coupling reaction at 90 °C, and they had to increase catalytic loading for the arylation of phenols with aryl bromide.¹⁵ The same catalyst (20 mol % *N,N*-dimethylglycine **L6**-CuI) provided only 55% yield for the coupling of iodobenzene and *p*-cresol in acetonitrile at 82 °C (Table 1, entry 8). Although β -keto ester¹⁷ as ligand with copper provided coupling reaction at 60–80 °C, requirement of high boiling solvent such as DMSO and limited substrate scope encourages for better alternative. Similarly, Salox ligand along with Cu₂O catalyzed the coupling reaction at 82 °C but needed longer reaction time (≥ 24 h), and particularly in the case of aryl bromide the reaction required higher temperature¹⁶ (110 °C).

3. Conclusion

In summary, we have described an efficient and experimentally simple copper-catalyzed *O*-arylation of phenols and aliphatic alcohols with aryl halides. The presence of an electron-releasing group in phenol increased the yield of the coupling reaction, whereas an electron-withdrawing group in aryl halide increased the yield of the coupling reaction. The presence of

an electron-releasing group such as a methoxy group in the *para* position of aryl halide decreased the yield of coupling reaction, whereas the presence of the same methoxy group at the *meta* position of aryl halide increased the yield. Less reactive aryl bromides can also be used for the *O*-arylation of phenols under the same reaction conditions without increasing the reaction temperature, catalyst loading, and time. The catalytic system not only is capable of coupling hindered substrate but also tolerates a broad range of a series of functional groups.

3. Experimental Section

General Procedure for the Coupling of Aryl Bromides and Iodides with Aromatic Phenols. Cs₂CO₃ (325.8 mg, 1 mmol), CuI (19 mg, 0.1 mmol), and **L3** (26.6 mg, 0.1 mmol) were taken in a 10 mL reaction tube equipped with a septum. The reaction tube was evacuated and backfilled with nitrogen. Dry acetonitrile (2.5 mL) was added to the reaction mixture at room temperature. To the resulting solution was added iodobenzene (102 mg, 0.5 mmol) followed by *p*-cresol (64.8 mg, 0.6 mmol), and the reaction mixture was heated for 17 h at 82 °C. After complete disappearance of iodobenzene (the progress of the reaction was followed by TLC), the reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The crude residue was directly purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford 1-phenoxy-4-methylbenzene¹⁵ (89.2 mg, 97%) as a colorless oil. *R*_f 0.73 (in hexanes); FTIR (neat) 1233, 2922, 3029 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.32 (s, 3H), 6.92 (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); ¹³C NMR (100 MHz, CDCl₃) δ 20.7, 118.3, 119.1, 122.8, 129.6, 130.2, 132.8, 154.7, 157.8; HRMS (MH⁺) calcd for C₁₃H₁₃O 185.0966, found 185.0974.

General Procedure for the Coupling of Aryl Iodides with Aliphatic Alcohols. An oven-dried screw-cap pressure tube fitted with a septum was charged with Cs₂CO₃ (325 mg, 1 mmol), CuI (19 mg, 0.1 mmol), **L3** (26.6 mg, 0.1 mmol), *p*-methoxyiodobenzene (117 mg, 0.5 mmol), and a magnetic stir bar. The pressure tube was evacuated and backfilled with anhydrous nitrogen. Ethanol (1.5 mL) was added, and the reaction mixture was stirred at 82 °C for 22 h (the progress of the reaction was followed by TLC). After the complete disappearance of *p*-methoxyiodobenzene (by TLC), the reaction mixture was allowed to cool to room temperature, and the crude product was purified by column chromatography on silica gel using ethyl acetate/hexane solvent mixture to give 4-ethoxyanisole²³ (73 mg, 92%) as a white solid; *R*_f 0.46 (in hexanes); FTIR (neat) 1229, 2929, 2980 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 1.38 (t, *J* = 6.8 Hz, 3H), δ 3.76 (s, 3H), 3.97 (q, *J* = 6.8 Hz, 2H), δ 6.83 (s, 4H); ¹³C NMR (100 MHz, CDCl₃) δ 15.1, 55.9, 64.2, 114.8, 115.7, 153.3, 153.9; HRMS [MH⁺] calcd for C₉H₁₃O₂ 153.0916, found 153.0916.

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Supporting Information Available: Experimental procedures and characterization data for all new and known compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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