BETTI BASE AS AN EFFICIENT LIGAND FOR COPPER-CATALYZED ULLMANN COUPLING OF PHENOL WITH ARYL HALIDES

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GRAPHICAL ABSTRACT

Abstract A simple, general, and highly efficient Betti base ligand has been developed for copper-catalyzed Ullmann coupling of phenol with aryl halides without the protection of an inert atmosphere. The reaction proceeds smoothly in the presence of K2CO3 as the base and dimethylsulfoxide as the solvent. The catalyst was reused several times with no evident loss of catalytic activity and is environmentally friendly.

Keywords Aryl halides; Betti base; copper; phenol; Ullmann coupling

INTRODUCTION

Diaryl ethers play an important part in many biologically active compounds and polymers and has applications in industrial and life sciences.[1–14] The traditional formation of C-O bond is the Ullmann reaction, which used aryl halide and phenol as substrates.[15] Subsequently, aryl acetate,[16–18] aryl boronic acid,[19–22] aryl siloxane,[23,24] and arylstannane[25] were introduced to react with phenol. However, these methods often suffered harsh reaction conditions, such as high temperature and the stoichiometric recyclable catalyst. Therefore, much effort has been devoted to developing more convenient methods of Ullmann-type O-arylation.

Because of the low cost, copper[26–30] was investigated as an alternative catalyst to palladium.[31–36] 1-Naphthoic acid,[37] 2,2,6,6-tetramethylheptane-3,5-dione,[38]...
1,10-phenanthroline, neocuproine, triphenylphosphine, N,N-dimethylglycine, 8-hydroxyquinoline, pyrrolidine-2-phosphonic acid phenyl monoester, 1,1'-binaphthyl-2,2'-diamine and (E)-3-(dimethylamino)-1-(2-hydroxyphenyl) prop-2-en-1-one have been used in these reaction as ligands. However, these ligands have major drawbacks of limited recyclability and difficult preparation. Herein, we report a simple and high-efficiency Betti ligand for copper-catalyzed Ullmann-type O-arylation to obtain these diaryl ethers. This catalyst system could be reused.

RESULTS AND DISCUSSION

The ligands were prepared by classical Mannich reaction (Fig. 1). The reaction could occur smoothly at room temperature. We tested the catalytic ability of these Betti bases in the O-arylation reaction catalyzed by CuI, and the results are presented in Table 1. The result showed that the ligand formed by pyridine aldehyde is more efficient than benzaldehyde (Table 1, entries 1–4 and 5–8). The reason may be that the pyridyl ligands has the capability to coordinate with metal centers to form a six-member stable cycle chelate and could coordinate with the metal center via the pyridyl nitrogen. We choose 1-(dimethylamino-1-yl-pyridin-2-yl-methyl)naphthalen-2-ol (L1) as the best ligand for the reaction.

Then, we further optimized the reaction conditions, and the results are listed in Table 2. The results showed that dimethylsulfoxide (DMSO) was the best solvent (Table 2, entry 1), and dimethylformamide (DMF) and toluene (Table 2, entries 2 and 7) provided lower yields when using H2O, N-methyl pyrrolidone (NMP), and 1,4-dioxane (Table 2, entries 3–5) as the solvents, no product was obtained. Interestingly, we also obtained desired product at the solvent-free condition (Table 2, entry 9).

Figure 1. List of ligands.
Among the various copper sources, the CuI was found to be the best catalyst (Table 2, entries 10–19), and Cu\(^+\) catalytic effect is better than the Cu\(^{2+}\) salt. There is no product without catalyst (Table 2, entry 19).

The influence of base was also screened: K\(_2\)CO\(_3\) showed more improvement than Cs\(_2\)CO\(_3\), K\(_3\)PO\(_4\), and KOH to give product 3\(a\) in 88\% yield. Some organic bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), triethylamine, and diethylamine showed no reactivity in this reaction (Table 2, entries 20–25). In addition, the yield was significantly decreased when the reaction was performed at the lower temperature (Table 2, entry 28). When changing the reaction time (Table 2, entries 26 and 27) the yield of the product was also reduced. Furthermore, no product was obtained without the participation of L\(_1\).

Under the optimized reaction conditions (Table 2, entry 1), we extended the scope of the substituted phenols (2) with iodobenzene (1\(a\)), and the results are summarized in Table 3. An electron-donating group of phenols reacted with iodobenzene in the presence of 0.1 mmol CuI, 0.2 mmol L\(_1\), and 2.0 equiv K\(_2\)CO\(_3\) in DMSO to give the corresponding diaryl ethers in excellent yields (Table 3, entries 1–7). Under the same reaction conditions, electron-withdrawing groups gave no yields (Table 3, entries 14–16). Notably, phenol with group of –OCH\(_3\), no matter ortho- or para-, display an effective effect with the yields 100\% (Table 3, entries 4 and 5). Entries 11–13 performed moderate in this reaction only with a yield of about 30\%, probably due to the steric hindrance.

To further reveal the scope of this catalyst system in the O-arylation reaction, various substituted aryl halides were coupled with phenol, and the results are summarized in Table 4. Generally, the reaction activities of chlorobenzene and bromobenzene are less (Table 4, entry 1). When substituted with electron-withdrawing groups, particularly nitro group, the reaction reacted smoothly with m-cresol to give a satisfactory product in a 99\% yield (Table 4, entries 2–6). Aldehyde and carbonyl substituted chlorobenzene and bromobenzene also afforded the corresponding diaryl ethers in excellent yields (Table 4, entries 7–9). However, a strong electron-donating group of aryl halides evidently restrained the coupling reaction (Table 4, entries 11

| Entry | L      | Yield (%) |
|-------|--------|-----------|
| 1     | L\(_1\) | 88        |
| 2     | L\(_2\) | 75        |
| 3     | L\(_3\) | 42        |
| 4     | L\(_4\) | 53        |
| 5     | L\(_5\) | 3         |
| 6     | L\(_6\) | 18        |
| 7     | L\(_7\) | 21        |
| 8     | L\(_8\) | 5         |
When using dichlorobenzene we observed no desired product in the reaction (Table 4, entry 10).

Finally, the reusability of the catalyst system was tested: The catalyst can be recovered and reused for five runs without any significant loss of catalytic activity for coupling reaction of iodobenzene with m-cresol (Table 5).

### EXPERIMENTAL

#### General Procedure for the Synthesis of Ligands

A solution of β-naphthol (1.0 g, 6.93 mmol) and aldehyde (0.74 g, 6.93 mol) in absolute alcohol (2 mL) was prepared. Amine (0.61 g, 6.93 mmol) was slowly added to this solution, and the mixture was stirred for 48 h at room temperature. Subsequently, the solid was filtered off and washed twice with cold ethyl alcohol (2–3 mL). It

| Entry | Solvent | Base    | Catalyst | Time (h) | Yield (%)a |
|-------|---------|---------|----------|----------|------------|
| 1     | DMSO    | K2CO3   | CuI      | 24       | 88         |
| 2     | DMF     | K2CO3   | CuI      | 24       | 36         |
| 3     | NMP     | K2CO3   | CuI      | 24       | 0          |
| 4     | H2O     | K2CO3   | CuI      | 24       | 0          |
| 5     | 1,4-Dioxane | K2CO3 | CuI      | 24       | 0          |
| 6     | THF     | K2CO3   | CuI      | 24       | 11         |
| 7     | Toluene | K2CO3   | CuI      | 24       | 32         |
| 8     | CH3CN   | K2CO3   | CuI      | 24       | 20         |
| 9     |         | K2CO3   | CuI      | 24       | 36         |
| 10    | DMSO    | K2CO3   | Cu power | 24       | 62         |
| 11    | DMSO    | K2CO3   | CuBr     | 24       | 50         |
| 12    | DMSO    | K2CO3   | CuCl     | 24       | 41         |
| 13    | DMSO    | K2CO3   | CuO      | 24       | 39         |
| 14    | DMSO    | K2CO3   | CuBr2    | 24       | 25         |
| 15    | DMSO    | K2CO3   | CuCl2·2H2O | 24     | 26         |
| 16    | DMSO    | K2CO3   | CuSO4    | 24       | 11         |
| 17    | DMSO    | K2CO3   | Cu(OAc)2·H2O | 24    | 35         |
| 18    | DMSO    | K2CO3   | CuO2     | 24       | 58         |
| 19    | DMSO    | K2CO3   | —        | 24       | 0          |
| 20    | DMSO    | KOH     | CuI      | 24       | 72         |
| 21    | DMSO    | K3PO4   | CuI      | 24       | 55         |
| 22    | DMSO    | Cs2CO3  | CuI      | 24       | 35         |
| 23    | DMSO    | DBU     | CuI      | 24       | 10         |
| 24    | DMSO    | Triethylamine | CuI | 24   | 0          |
| 25    | DMSO    | Diethylamine | CuI | 24   | 0          |
| 26    | DMSO    | K2CO3   | CuI      | 36       | 62         |
| 27    | DMSO    | K2CO3   | CuI      | 20       | 60         |
| 28    | DMSO    | K2CO3   | CuI      | 24       | 2c        |
| 29    | DMSO    | K2CO3   | CuI      | 24       | 0d        |

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aReaction conditions: iodobenzene (1.0 mmol), m-cresol (1.0 mmol), CuX (0.1 mmol), L (0.2 mmol), 2.0 equiv base, solvent (3 mL), 120°C.

bGC yield determined by using methoxybenzene as internal standard.
cReaction temperature is 80°C.
dWithout L.
Table 3. Copper-catalyzed O-arylation of phenols with iodobenzene<sup>a</sup>

| Entry | Phenol | Product | Yield (%)<sup>b</sup> |
|-------|--------|---------|-----------------------|
| 1     | ![Phenol](image1) | ![Product](image2) | 88                    |
| 2     | ![Phenol](image3) | ![Product](image4) | 87                    |
| 3     | ![Phenol](image5) | ![Product](image6) | 88                    |
| 4     | ![Phenol](image7) | ![Product](image8) | >99                   |
| 5     | ![Phenol](image9) | ![Product](image10) | >99                   |
| 6     | ![Phenol](image11) | ![Product](image12) | 90                    |
| 7     | ![Phenol](image13) | ![Product](image14) | 91                    |
| 8     | ![Phenol](image15) | ![Product](image16) | 65                    |
| 9     | ![Phenol](image17) | ![Product](image18) | 35                    |
| 10    | ![Phenol](image19) | ![Product](image20) | 58                    |

(Continued)
was recrystallized from a mixture of petroleum ether and ethyl acetate to get colorless crystals of L ligands.

**General Procedure for the Synthesis of Coupling Products**

All reactions were carried out under air. Aryl halides (1.0 mmol) were treated with phenol (1.0 mmol) in the presence of 0.1 mmol CuI, 0.2 mmol 1-(α-aminobenzyl)-2-naphthols and 2.0 equiv K₂CO₃, DMSO (3 mL), 120 °C for 24 h. The progress of the reaction was monitored by gas chromatography (GC). After completion of the reaction, the catalyst was filtered easily and the product was extracted with EtOAc, The combined organic layers were dried over MgSO₄.
Table 4. Copper-catalyzed O-arylation of m-cresol with aryl halides

| Entry | Ar-X | Product | Yield (%)<sup>b</sup> |
|-------|------|---------|-----------------------|
| 1     | ![aryl halide](image1) | ![product](image2) | 1: 88  
Br: 0  
Cl: 0 |
| 2     | ![aryl nitro](image3) | ![product](image4) | >99 |
| 3     | ![aryl nitro](image5) | ![product](image6) | >99 |
| 4     | ![aryl nitro](image7) | ![product](image8) | >99 |
| 5     | ![aryl nitro](image9) | ![product](image10) | >99 |
| 6     | ![aryl nitro](image11) | ![product](image12) | >99 |
| 7     | ![aryl chloride](image13) | ![product](image14) | 70 |
| 8     | ![aryl chloride](image15) | ![product](image16) | 69 |
| 9     | ![aryl bromide](image17) | ![product](image18) | 71 |

(Continued)
for 12 h. The solvent was evaporated under reduced pressure and the desired product was purified by flash chromatography on a silica-gel column using petroleum ether/ethyl acetate (10:1).

In summary, we have developed a practical CuI-Betti base ligand for copper-catalyzed coupling of a variety of phenol and aryl halides. The ligands are easy to synthesize and the reaction can proceed smoothly without the protection of an inert atmosphere. The catalytic system can be recycled and is environmentally friendly.

**SUPPORTING INFORMATION**

Supplemental data for this article can be accessed on the publisher’s website.

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