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## Ullmann C–O Coupling of Sterically Hindered Secondary Alcohols Using Excess Amount of Strongly Coordinating Monodentate Ligands

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#### ABSTRACT

A new effective copper catalyzed C-O coupling reaction using excess amount of strongly coordinating monodentate ligands was successfully developed. Among the DMAP-type monodentate ligands, 4-pyrrolidinopyridine afforded the best results. The developed reaction is widely applicable for the synthesis of various hindered or acyclic secondary alkyl-aryl ethers. In this study, a novel and remarkable acceleration of the coupling reaction using excess amount of monodentate ligands was discovered.

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#### Introduction

Copper-promoted C-O coupling reaction has been widely used in synthetic organic chemistry.1 The originally reported Ullmann coupling reaction<sup>2</sup> was conducted in the presence of a stoichiometric amount of copper salt and limited to the construction of biaryl ether linkages.<sup>3</sup> In 2002, Buchwald and coworkers reported the first catalytic reaction of aliphatic alcohols with aryl halides using 1,10-phenanthroline as a bidentate ligand.<sup>4</sup> The reaction conditions were then modified<sup>5</sup> and applied to the synthesis of various alkyl aryl ethers, in good yields, when used for the C-O coupling reactions of primary or cyclic secondary alcohols.<sup>6</sup> This useful etherification procedure was recently applied successfully for the direct construction of highly strained 13-membered macrocycle of Hirsutellone B;<sup>7</sup> however, for sterically-hindered or acyclic secondary alcohols, the etherification procedure often afforded unsatisfactory results. In this study, we attempted to develop a new Ullmann-type C-O coupling reaction for these less reactive substrates.

#### **Results and discussion**

We first examined the reaction of aryl iodide 1a with  $\beta$ cholestanol 2a, used as a model substrate for sterically-hindered secondary alcohols, under various conditions (Table 1).

#### Table 1

Reaction of a hindered secondary alcohol with an aryl iodide under different conditions.



Entry	Conditions	Yield (%)			
		3	4	5	2 (recovered)
1	L1, Cs <sub>2</sub> CO <sub>3</sub> , 110 °C	21	2	2	67
2	L1, Cs <sub>2</sub> CO <sub>3</sub> , 140 °C	45	2	50	0
3	L2, Cs <sub>2</sub> CO <sub>3</sub> , 140 °C	47	2	0	49
4	L2, <i>t</i> -BuONa, 140 °C	9	0	0	38
5	L2, <i>t</i> -BuOK, 140 °C	15	0	0	32
6	L2, K <sub>2</sub> CO <sub>3</sub> , 140 °C	8	0	0	90
7	L2, Li <sub>2</sub> CO <sub>3</sub> , 140 °C		NR		quant.
8	<b>L2</b> , K <sub>3</sub> PO <sub>4</sub> , 140 °C	48	0	0	51

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However, the desired coupling product 3a was obtained in poor yield (21%) under the reported reaction condition<sup>3</sup> using 3,4,7,8-tetramethyl-1,10-phenanthroline (Me<sub>4</sub>-phen, L1, Entry 1). In this case, the reduced side product 4a, from aryl iodide 1a, was also obtained with 2% yield. The reaction temperature was found to be a very important parameter. When the reaction was conducted at 140 °C, the yield of 3a improved to 45%; however, side product 5a was also obtained in larger quantities (50%, Entry 2). This undesired side reaction was completely eliminated using unsubstituted 1,10-phenanthroline (phen, L2, Entry 3) as a ligand.<sup>4</sup> Although the use of cesium carbonate (Cs<sub>2</sub>CO<sub>3</sub>) afforded a trace amount of 4a as another side product, various inorganic bases were screened. As a result, potassium phosphate (K<sub>3</sub>PO<sub>4</sub>) was employed as the most suitable base. However, we could not obtain satisfactory results using these minor improvements in the reported reaction conditions.

Previous excellent studies on the Ullmann C–O coupling reaction mechanism<sup>8,9</sup> have reported the formation of a three-coordinate copper (I) alkoxide complex (**Ia**) to have occurred earlier than the activation of aryl halide (Fig. 1).



**Fig. 1.** Plausible mechanism of Ullmann C-O coupling reaction utilizing a bidentate ligand.

In the experiments described above, two equivalents (vs copper atom) of bidentate L2 ligand were used according to the reported procedure.<sup>4,5</sup> In this reaction condition, a four-coordinate cationic copper complex IIa should be formed first because the 18-electron complex IIa is coordinatively stable and has good solubility in the reaction solvent.<sup>10</sup> Therefore, it was assumed that the active species of this type of coupling reactions should be generated *via* complex IIa.<sup>11</sup> If the precise active species of the next halide activation process is a three-coordinate copper alkoxide complex Ia, it should be produced via a nucleophilic attack of the substrate alkoxide on the complex IIa to afford a relatively unstable five-coordinate copper (I) complex IIIa<sup>12</sup> and subsequent elimination of one equivalent of L2. However, when L2 type of bidentate ligands are used in the reaction, this elimination process becomes unfavorable because the complex IIIa is stabilized by the chelation effect of bidentate ligands. Therefore, we explored a new reaction condition that uses an "easily dissociating" monodentate ligand (Figure. 2).



**Fig. 2.** Proposed mechanism of Ullmann C-O coupling reaction utilizing a monodentate ligand.

The monodentate ligand can cause a fast equilibrium between complexes **IIIb** and **Ib**. Therefore, the active species **Ib** would be smoothly produced, proceeded by the next halide activation. In addition, the strong coordinating ability of monodentate ligand can provide a more electron-rich and reactive three-coordinate copper alkoxide complex **Ib** for the halide activation process.

This type of Ullmann C–N and C–O coupling reaction using a 4-(N,N-dimethylamino)pyridine (DMAP)-type monodentate ligand was reported by Wong and co-workers;<sup>13-15</sup> however, the reported examples of C–O coupling reaction in this study were limited to the formation of biaryl ether linkages. Therefore, we examined this reaction for the existing model reaction to form a hindered alkyl–aryl–ether linkage (Table 2).



C-O coupling reactions with monodentate and bidentate ligands.

1a + 2a	Ligand Cul (10 mol%), K <sub>3</sub> PO <sub>4</sub> (200 mol%)	39	`N∕
	toluene, 140 °C		N
	18 hr		DMAP (L3)

Entry	Ligand (mol%)	Yield (%)		
	-	3a	2a (recovered)	
1	L3 (40)	40	56	
2	L2 (20)	48	51	

Contrary to our expectation, the model reaction using 40 mol% of DMAP (L3) with 10 mol% of CuI gave a rather poor yield (40%, Entry 1) compared with that of using 20 mol% of L2 (48%, Entry 2). However, we gradually increased the amount of L3 because the monodentate ligands can easily dissociated upon heating and the desired copper (I) alkoxide complex might not be generated in a sufficient equilibrium concentration. In the course of these experiments, we discovered an unprecedented and remarkable improvement in the reaction rate and yield by using an excess amount of the monodentate ligands, i.e., the yield of the coupling product **3a** improved with an increase in the amount of ligand, reaching up to 76% yield with 120 mol% of L3 (Table 3, Entry 1-7).

#### Table 3

Effect of the amount of L3

and screenings of 4-substituted pyridine-type monodentate ligands and solvents.



Entry	Ligand (mol%)	Solvent	Yield (%)
1	L3 (40)	toluene	40
2	L3 (60)	toluene	48
3	L3 (80)	toluene	65
4	L3 (100)	toluene	71
5	L3 (120)	toluene	76
6	L3 (140)	toluene	75
7	L3 (160)	toluene	74
$8^a$	L3 (120)	toluene	NR
9	L4 (40)	toluene	13
10	L4 (120)	toluene	36
11	L5 (40)	toluene	22
12	L5 (120)	toluene	58
13	L6 (120)	toluene	83
14	L7 (120)	toluene	72
15	L6 (120)	DMF	45
16	L6 (120)	DMSO	46
17	L6 (120)	chlorobenzene	75

<sup>*a*</sup> The reaction was conducted in the absence of  $K_3PO_4$ . DMF = *N*,*N*-dimethylformamide. DMSO = dimethyl sulfoxide.

This acceleration of the reaction rate obtained on using an excess amount of L3 is clearly demonstrated through a kinetic analysis of this reaction (Figure. 3).



Fig. 3. Kinetic analysis of the C-O coupling reaction using an excess amount of monodentate ligand.

The initial reaction rate (0 to 2 h) for this reaction with 120 mol% of L3 is approximately three times faster than that using 20 mol% of L2. In contrast, in the presence of 60 mol% of L2, the same fraction of coordinating nitrogen atoms as 120 mol% of L3, the yield of the coupling product 3a (9%) was apparently lowered. Such a specific and significant acceleration of the reaction rate on using excess amount of monodentate ligand has not been reported in studies on copper catalyzed C-O or C-N coupling reactions.

We next screened other 4-substituted pyridine type monodentate ligands such as 4-methylpyridine (L4) and 4methoxypyridine (L5) (Table 3, Entry 9-14). A similar acceleration was observed on using one of these ligands, but the acceleration gradually lowered with the decreasing electron donating ability of the 4-substituent on the pyridine ring (Entry 9-10 and 11-12). In contrast, the use of 4-(N,N-disubstituted amino)pyridines afforded good results for each case, with 4pyrrolidinopyridine (L6) affording the best yield (83%, Entry 13). In the case of using more hindered 9-azajulolidine (L7), which is the best ligand as per Wong's report,<sup>13</sup> the yield was lowered (Entry 14). These results indicated that strongly coordinating and less sterically hindered ligands are very important for the observed acceleration in the reaction rate. The solvent effect was also examined in the C-O coupling reaction with the best ligand (L6), and toluene was superior to other more polar solvents (Table 3, Entry 15-17).

The coupling reactions of various sterically hindered alcohols (2b-i) with iodobenzene 1b using 120 mol% of L6 and 10 mol% copper (I) iodide are demonstrated (Table 4).

### Table 4



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<sup>a</sup> Reactions conducted using the phen ligand; CuI (10 mol%), L2 (20 mol%), Cs<sub>2</sub>CO<sub>3</sub> (200 mol%), toluene, 140 °C, 18 h.

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The desired alkyl aryl ethers **3b-i** were obtained from sterically hindered primary and secondary alcohols in good to high yield for each case. Specifically, in the reaction of acyclic secondary alcohols, the yields were greatly improved compared with those that used the bidentate ligand (**L2**) (Entry 3-6). In addition, no racemization of the stereogenic center of (R)-2-phenylethanol was observed in the coupling reaction (Entry 8).

Thus, we developed a new, effective copper catalyzed C–O coupling reaction using an excess amount of strongly coordinating monodentate ligand. Therefore, we considered the advantage of using an excess amount of monodentate ligand. An interesting report concerning the chemical property of the three-coordinate copper phenoxide complex **Ic** was presented by Hartwig and co-workers.<sup>16</sup> According to this study, the complex **Ic** is in equilibrium with a polarized binuclear complex **IVc** through a disproportionation process (Scheme 1).



Scheme 1. Hartwig's reported equilibrium between polarized binuclear complex IVc and tricoordinate alcoxide complex Ic.

In addition, independently prepared binuclear complex **IVd** is found to be less reactive toward aryl halides in the absence of a **L2** than in the presence of **L2** (Scheme 2).



Scheme 2. Hartwig's reported effect of bidentate phen ligand reactivity of polarized complex IVd.

These Hartwig's observations indicated that coordination of phen ligand (L2) toward the negatively charged copper atom of the polarized binuclear complex IVc afford the active species for the next halide activation, and it should be the three-coordinate copper alkoxide complex Ic. Putting all this together, excess amount of monodentate ligands would produce a new fast equilibrium between three kinds of copper species as shown in Scheme 3. As a result, the reactive three-coordinate copper alkoxide complex Ib could be more smoothly provided from the less reactive polarized binuclear complex IVb through the equilibrium.<sup>17</sup>



Scheme 3. A plausible equibrium between three kinds of copper species in the presence of excess amount of monodentate ligands.

#### Conclusions

In conclusion, a new effective copper catalyzed C–O coupling reaction using excess amount of a strongly coordinating monodentate ligand was successfully developed. The reaction is widely applicable for the construction of hindered or acyclic secondary alkyl–aryl ether linkages. In the course of this study, a novel and remarkable acceleration in the rate of reaction through the use of excess amount of monodentate ligand was discovered. This new finding may bring further evolution in transition metal catalyzed synthetic reactions using coordinatively unsaturated active species. Synthetic studies of some natural compounds with interesting biological activity utilizing this new etherification procedure are now in progress.

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#### Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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- Accepted NAMESCRIP 17. Hartwig et al. also reported that the equilibrium as shown in Scheme 1 significantly shifted to the polarized binuclear complex IVc by using polar solvent such as DMSO.<sup>16</sup> This observation well agreed with our

Tetrahedron

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### HIGHLIGHTS

A new effective copper catalyzed C-O coupling reaction is successfully developed.

A remarkable acceleration by using excess amount of monodentate ligands is observed.

Various hindered or acyclic secondary alkyl-aryl ethers are obtained in high yields.

Advantages on the reaction mechanism by using excess amount of ligands are discussed.

### **Graphical Abstract**

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