Preprint Title	Efficient pyrazole moiety-containing ligands for Cu-catalyzed *O*-arylation of phenols
Authors	Yingying Zhao, Xiangyong Wang, Ryo Kaneyama, Koichi Kodama and Takuji Hirose
Publication Date	29 Aug 2019
Article Type	Full Research Paper
Supporting Information File 1	Supporting Information File 1 (2CuL1).cif; 171.8 KB
Supporting Information File 2	Supporting Information File 2 (CuBrL6).cif; 270.4 KB
Supporting Information File 3	Supporting Information File 3.docx; 409.9 KB
Supporting Information File 4	Supporting Information File 4.doc; 2.1 MB
ORCID® iDs	Takuji Hirose - https://orcid.org/0000-0003-4121-0963

Efficient pyrazole moiety-containing ligands for Cu-catalyzed *O*-arylation of phenols

Yingying Zhao,[1] Xiangyong Wang,[1] Ryo Kaneyama,[1] Koichi Kodama,[1] and Takuji Hirose[1*]

Address: [1]Graduate School of Science & Technology, Saitama University, Shimo-ohkubo, Sakura, Saitama, Saitama 338-8570, Japan

Email: Takuji Hirose - hirose@apc.saitama-u.ac.jp

* Corresponding author

Abstract

Seven N_2- and N_3-ligands (**L1**–**L7**) were developed for the ligand-assisted CuI-catalyzed coupling reactions of aryl halides with phenols. The structural and electronic effects were studied for various combinations of pyridine and/or imine nitrogen binding sites in the ligands. 2-(1-Pyrazolyl)pyridine (**L1**) featuring two types of binding sites gave the best results, with yields of up to 90% at 100 °C at a catalyst loading of 10 mol% (CuI/**L** in 1:1 ratio). A non-radical mechanism, proposed for the **L1**-promoted coupling reaction, well explained the different effects of electronic nature of the substituent and steric hindrance on phenols and aryl halides.

Keywords

2-(1-Pyrazolyl)pyridine; CuI; Diaryl ether; Cross coupling; non-radical mechanism

Introduction

Diaryl ethers are crucial structural motifs in natural products as well as synthetic compounds [1-9], including antibiotic vancomycin [6,7], perrottetines [8], and chloropeptins (anti-HIV agents) [9]. Therefore, effective methods for the synthesis of diaryl ether bridges are highly desired. Although the classical Ullmann coupling reaction has been used successfully for the arylation of phenols with aryl halides in the presence of copper or copper salts, the required harsh reaction conditions have hindered its widespread promotion and industrialization [10-12].

In the past two decades, much effort has been devoted to the development of efficient methods for the synthesis of diaryl ethers. The introduction of ligands into Pd-catalyzed C–O coupling reactions successfully overcame the limitations of the classical Ullmann coupling reaction [13-15]. Although there has been tremendous development in Pd-catalyzed C–O bond formation reactions, copper has not been replaced and is still widely used as an economical and less-toxic catalyst [16,17]. Research interest in copper-assisted *O*-arylation coupling reactions was aroused by the discovery of certain effective copper catalyst systems, such as combinations of copper salts with bidentate ligands, which enable the execution of coupling reactions under relatively mild conditions [17-23].To date, a number of nitrogen-containing ligands, such as bipyridine [23-25], 1,10-phenanthroline [25-27], salicylaldoxime [28], glyoxal bis(phenylhydrazone) [22], 2-(phenyliminomethyl)pyridine [25], and *trans*-1,2-bis(2′-pyridylidenamino)cyclohexane (Chxn-Py-Al) [28,29], have been applied successfully to Cu-catalyzed arylation under mild conditions. However, some relatively expensive reagents, such as $Cu(CH_3CN)_4BF_4$ [24], Cu/C [26], and $CuI/KF/Al_2O_3$ [27], and moisture-sensitive Cs_2CO_3 [26,28] are often required for highly efficient *O*-arylation. In our previous work [30], we comprehensively studied some typical bidentate ligands and found that electron-rich 4,4′-dimethoxy-2,2′-bipyridine and 4,7-dimethoxy-1,10-phenanthroline afforded higher yields than those of simple bipyridine and phenanthroline under typical reaction conditions, using CuI and K_3PO_4 as the catalyst and base, respectively. However, the exploration of new ligands is still necessary to promote the reaction with less amount of a catalyst.

Taillefer and co-authors investigated several bidentate N_2-ligands and reported that unsymmetric 2-(phenyliminomethyl)pyridine showed high catalytic activity in Cu-catalyzed *O*-arylation owing to the combination of two different coordination moieties (pyridine and imine) [25]. They stated that the pyridine nitrogen atom could make the Cu atom more electron-rich, facilitating the oxidative addition to aryl halides, whereas the imine nitrogen atom may make the Cu atom more electron-poor, facilitating the reductive elimination to the products [25]. Their results motivated us to apply their design concept to aromatic moieties. The objective of this study is to apply new N_2- and N_3-ligands composed of two different heteroaromatic structures, pyridine and pyrazole, to the CuI-catalyzed C-O coupling reaction.

Pyrazoles have been used successfully as *N*-donor ligands for transition metals (Pd, Fe, Co, Ru, Cu, and Ni) in C–C coupling reactions [31,32]. However, for C–O coupling reactions, the application of metal complexes with pyrazole-containing ligands has not received enough attention thus far [28]. The basicity for a pyrazole nitrogen (N_{pz}: $pK_a = 2.47$) is somewhat weaker than that of the pyridine nitrogen (N_{py}: $pK_a = 5.23$), which may be similar to that of 2-(phenyliminomethyl)pyridine derived from 2-pyridylcarboxaldehyde and aniline [25,33]. Moreover, proper disposition of coordinating atoms is important to enhance the efficiency of the metal/ligand-catalyzed reaction by stabilizing the complex. In view of the fact that nitrogen-containing ligands play an indispensable role in Ullmann-type coupling reactions [34], we also investigated several new ligands, copper salts, and reaction conditions.

Herein, we report the application of a series of ligands containing the pyrazole moiety (**L1**–**L3**) and their activities in Cu-catalyzed *O*-arylation, as well as the ligands (**L4**–**L7**) featuring only the pyridine moiety (Figure 1). For comparison, an efficient symmetric N_2-ligand, 4,4′-dimethoxy-2,2′-bipyridine (**L8**) [30], was also investigated in this study.

Results and Discussion

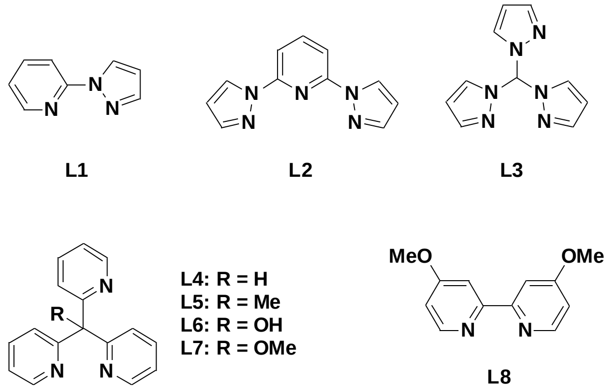
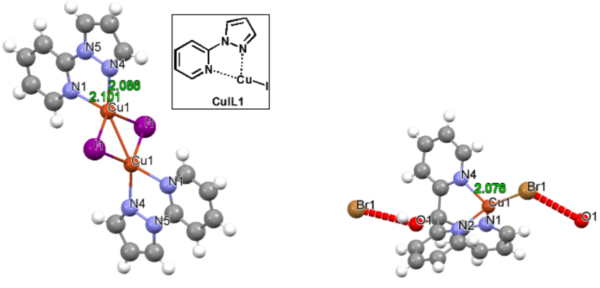


Figure 1: Structures of the ligands studied.

L1 was chosen as an asymmetric N_2-ligand having both N_{py} and N_{pz} atoms and was employed in the preparation of a complex with CuI in acetonitrile. As shown in Figure 2a, single-crystal X-ray analysis revealed the dimeric form of a CuI·**L1** 1:1 complex (Support Information Files 1 and 3). On the other hand, **L2** and **L3**, which contain two and three N_{pz} atoms, respectively, were expected to act as both N_3-ligands and N_2-ligands; therefore, their Cu complexes were more stable than that of **L1** because of the presence of an additional coordinating N atom. The three pyrazole-containing ligands (**L1**–**L3**) are not only commercially available, but also easy to prepare [35-37].To determine whether pyridyl N_3-ligands are effective for the reaction, **L5**–**L7** were prepared by quaternizing the aliphatic carbon of **L4**, which was also expected to serve as a N_3-ligand and a N_2-ligand similar to **L3**. On the other hand, all three N_{py}

atoms of **L5**–**L7** seemed to be able to coordinate with Cu owing to the quaternary carbon. In fact, the crystal structure of the CuBr complex of **L6** revealed that its three pyridine moieties coordinated to the same Cu atom in the polymeric form (Figure 2b, Support Information Files 2 and 3). To the best of our knowledge, no study has reported the activities of these seven ligands in *O*-arylation.



[CuI**L1**]$_2$
a

CuBr**L6**
b

Figure 2: (a) Single-crystal structure of the dimer of the CuI·**L1** 1:1 complex. Inset: Proposed active complex of **L1** and CuI. (See Supporting Information Files 1 and 3) (b) Crystal structure of the polymeric CuBr·**L6** 1:1 complex containing halogen-hydrogen bond [38]. (Supporting Information Files 2 and 3)

In order to investigate the potential of the ligands, the arylation of *p*-cresol with 4-iodotoluene was studied at 100 °C in DMSO in the presence of 10 mol% CuI and 10 mol% ligand, which are 50% and 75% lower than the amounts used for several bipyridine derivatives in our previous work, respectively [30]. The results are summarized in Figure 3. It is clear that **L1** efficiently promoted the coupling reaction by affording 90% yield of **3a**, which was much higher than that obtained with no ligand (55%) (Table S2, entries 2 *vs.* 1). In order to examine the catalytic activity of [CuI·**L1**]$_2$ (Figure 2a), a control experiment was conducted with the pre-formed complex equivalent of 10 mol% CuI. As shown in entry 3 of Table S2, a comparable yield of 89% was obtained. It can be considered that [CuI·**L1**]$_2$ was symmetrically divided into two units, *i.e.*, 2[CuI·**L1**] (Inset of Figure 2a), under highly polar and high temperature reaction conditions.

Another new ligand containing two pyrazole groups, 2,6-di(1-pyrazolyl)pyridine, **L2**, was found to be unexpectedly less efficient (63% yield) than **L1** as seen in Figure 3 (Table S2, entries 4 *vs.* 2). Due to the rigid bonds between the pyridine and pyrazole moieties, **L2** served as a N_2-ligand, identical to **L1**, however, the non-binding pyrazole moiety might limit the interaction with the substrate. On the other hand, **L3** having three pyrazole moieties gave a good yield of 81%, which was much higher

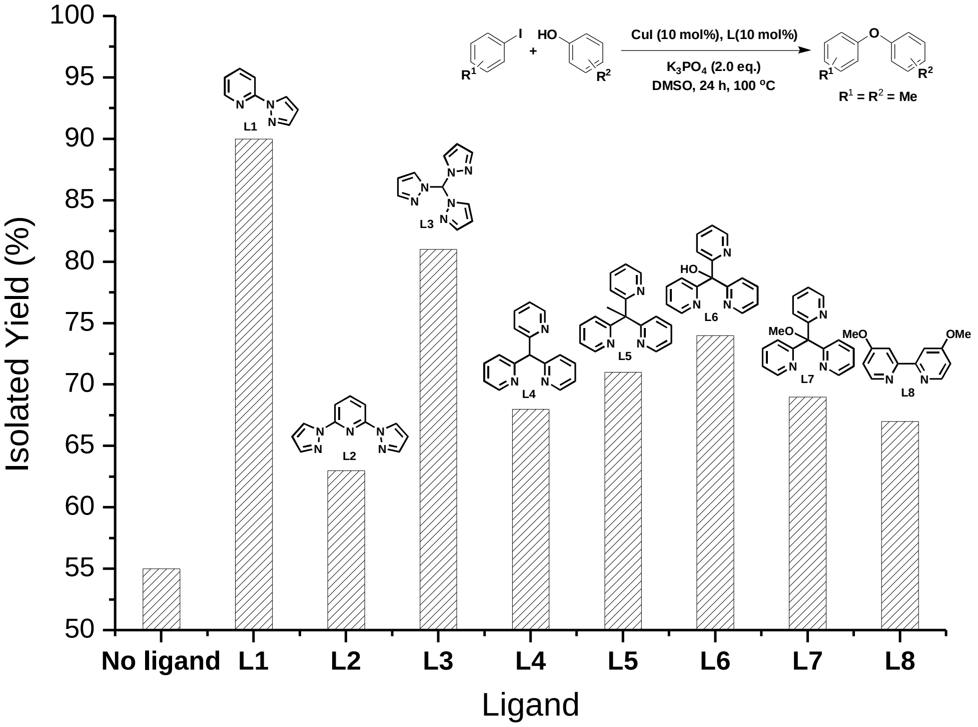


Figure 3: Comparison of various N_2- and N_3-ligands, **L1**–**L8**, for coupling of 4-iodotoluene with *p*-cresol.[a]

[a]Reaction conditions: **1a** (1 mmol), **2a** (1.5 mmol), CuI (0.1 mmol), ligand (0.1 mmol), K_3PO_4 (2.0 mmol), DMSO (7 mL), reaction time (24 h) and temperature (100 °C). [b]Isolated yield. [c][CuI·**L1**]$_2$ 0.05 mmol.

than that obtained using **L2** (Table S2, entries 5 *vs.* 4) and about 10% lower than that using **L1**. It is likely that two N_{pz} atoms of **L3** effectively coordinate with Cu, and a non-coordinating pyrazole moiety may be located apart from the Cu atom because of the mobility around the tertiary carbon connecting the pyrazole moieties. The activity of **L4**–**L7** featuring three pyridine moieties was also evaluated, and these ligands gave yields of around 70% as seen in Figure 3 (Table S2, entries 6–9). Considering the structures, however, the coordination mode of **L4** may be the same as **L3** but different from that of **L5**–**L7**, *i.e.*, only two N_{py} atoms of **L4** could coordinate strongly and the other pyridine moieties may not contribute efficiently. On the other hand, **L5**–**L7** worked as N_3-ligands as shown by the crystal structure of CuBr·**L6** in Fig. 2b. In any case, considering the lower yields for **L4**–**L7** than those obtained for **L1** and **L3**, the more flexible but bulky dipyridylmethyl structure seems less favorable. In addition, although **L5**–**L7** have different substituents on the quaternary carbon, the nature of these substituents most likely did not affect the activity of the ligands (Table S2, entries 7–9). Although additional N_{py} coordination in **L5**–**L7** stabilized the Cu complexes more, it caused steric hindrance in the following reaction, leading to a yield similar to that of **L4**. That is, this structural modification may have positively and negatively contributed to the reaction, leading to results similar to those for **L4**–**L7**.

In order to understand the characteristics of **L1** that make it the best ligand, **L8**, as the most efficient bipyridine ligand [30], was applied under the same reaction conditions. As shown in Figure 3, **L8** gave a 23% lower yield than that of **L1** (Table S2, entries 10 *vs.* 2), although it afforded ~90% yield when four times more of its amount (40 mol%) was used with 20 mol% CuI [30]. This reveals that the combination of pyrazole and pyridine moieties as a N_2-ligand is highly efficient for the *O*-arylation reaction. Moreover, new N_3-ligands **L4**–**L7** afforded yields comparable to that obtained using **L8**, which were much higher than that using the simple 2,2′-

bipyridine [30]. Therefore, the appropriately arranged three pyridine moieties effectively work for the reaction.

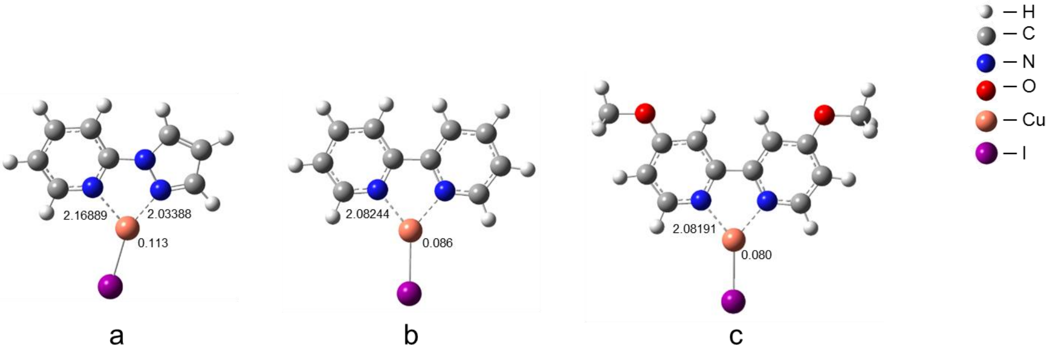


Figure 4: Structures of monomeric complexes of (a) **L1**, (b) bipyridine (**bpy**) and (c) **L8** with CuI, calculated using density functional theory (DFT).

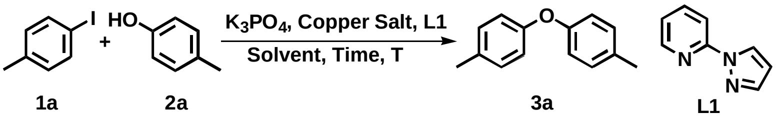
L1, which has a weaker electron-donating atom, N_{pz}, with a stronger one, N_{py}, was more effective than electron-rich **L8** in the coupling reaction. This result seems to contradict the conventional notion that a more stable complex catalyst is beneficial for coupling processes [39,40]. To clarify the difference in the ligand electronic properties, the atomic charges of the monomeric CuI·**L1** 1:1 complex, derived from the crystal structure of the 2:2 complex (Figure 2a), were calculated; the optimized structure is depicted in Figure 4a. The corresponding complexes of bipyridine (**bpy**) and **L8**, derived using the density functional theory, were also calculated and compared in Figure 4. The Cu atom in the CuI·**L1** complex has a positive charge of 0.113 $|e^-|$ (Figure 4a), whereas the Cu atoms in the **bpy** and **L8** complexes have lower positive charges of 0.086 $|e^-|$ and 0.080 $|e^-|$ (Figures 4b and 4c), respectively. The relationship between **bpy** and **L8** corresponded to that between their reported oxidation potentials [25].

The calculation suggests the Cu atom in its **L8** complex is easier to oxidize than that in the **bpy** complex, which leads to a higher reaction yield of the *O*-arylation. On the other hand, compared to CuI·**L8**, the positive electron density of the Cu atom of the **L1** complex is about 40% higher, whereas the yield is more than 20% higher. This indicates that the Cu atom in the **L1** complex behaves quite differently from that in the complexes of bipyridine–type ligands, which agrees with the discussion by Taillefer *et al*. [25] They observed the opposite substituent effect for imino pyridine and bipyridine ligands and elucidated it through the oxidative addition–reductive elimination mechanism [25,41].Our calculation data support the discussion; that is the asymmetric ligand complexes can be used in the reductive elimination step because the CuI·**L1** complex is effective for the reductive elimination or less active for oxidation due to its higher positive charge. On the other hand, the CuI·**L8** complex is effective for the oxidative addition step because of its lower positive charge.

Thus, with **L1** as a suitable ligand, the reaction parameters of the model reaction were optimized. The results are summarized in Table 1. First, the effect of the solvent was studied with CuI as the catalyst (entries 1–5). When the reaction was carried out in various solvents, namely 1,4-dioxane, toluene, CH_3CN, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO), the isolated yields of **3a** ranged from 29% to 90%, which indicates that the nature of the solvent has a significant influence on the coupling reaction. The best yield of 90% was obtained when the reaction was performed in DMSO at 100 °C (entry 5). The effectiveness of the solvents decreased in the following order: DMSO > DMF > toluene > 1,4-dioxane > CH_3CN. According to previous reports [42,43], the reaction intermediates exist in the equilibrium between neutral and ionic forms in the reaction solution, and the neutral form is favored in non-polar solvents, whereas the ionic form is favored in polar solvents.

Considering the excellent performance of DMSO with the highest polarity (ε = 46.5), the formation of ionic intermediates is crucial to the process than that of neutral intermediates. Likewise, a polar solvent is reasonably favorable for CuI and K_3PO_4, which are ionic compounds and more soluble in polar solvents such as DMSO and DMF [45]. For CH_3CN, the limitation of the reaction temperature of 82 °C [44] may be the main reason for the lowest yield in spite of its polarity (ε = 35.9) (entry 3).

Table 1: Effect of solvent, copper salt, temperature, and reaction time on the coupling of 4-iodotoluene with *p*-cresol.[a]



Entry	Solvent [ε] [44][b]	Copper source	Time (h)	T (°C)	Yield (%)[c]
1	1,4-dioxane [2.21]	CuI	24	100	39
2	toluene [2.38]	CuI	24	100	64
3	CH_3CN [35.94]	CuI	24	reflux[d]	29
4	DMF [36.71]	CuI	24	100	82
5	DMSO [46.45]	CuI	24	100	90
6	DMSO	CuBr	24	100	66
7	DMSO	CuCl	24	100	66
8	DMSO	CuSCN	24	100	84
9	DMSO	Cu_2O	24	100	47
10	DMSO	CuI	24	90	67
11	DMSO	CuI	24	120	89
12	DMSO	CuI	22	100	81
13	DMSO	CuI	20	100	79

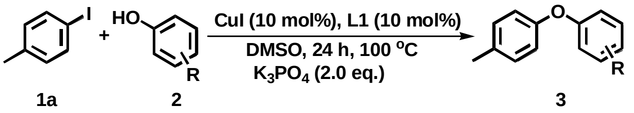
[a]General conditions: **1a** (1.0 mmol), **2a** (1.5 mmol), CuI (0.1 mmol), **L1** (0.1 mmol), K_3PO_4 (2.0 mmol). [b]ε = dielectric constant. [c]Isolated yield. [d]82 °C [44].

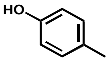
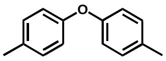
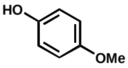
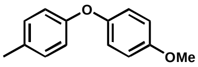
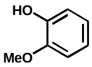
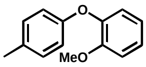
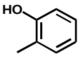
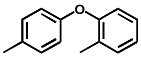
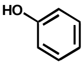
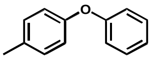
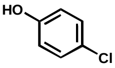
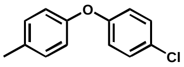
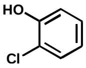
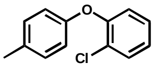
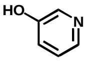
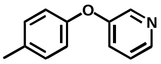
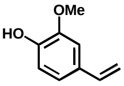
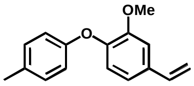
Five Cu(I) sources were then screened as catalysts in DMSO at 100 °C as shown in Table 1, entries 5–9. The results revealed that CuI is an excellent catalyst for the coupling reaction (entry 5), whereas CuBr and CuCl exhibited lower performance of 66% under the same reaction conditions (entries 6 and 7). In addition, two other cuprous sources, CuSCN and Cu_2O, afforded **3a** in 84% and 47% yields, respectively (entries 8 and 9). From the results, the counter anion species also considerably affects the reactivity of the copper complex, and a hydrophobic anion seems favorable.

Finally, we investigated the influence of reaction temperature and time on the coupling reaction. The effect of temperature on the yield can be observed in entries 5, 10, and 11: the yield decreased from 90% to 67% when the temperature was lowered from 100 °C to 90 °C (entries 5 and 10). In contrast, the yield showed no obvious change when the temperature was increased from 100 °C to 120 °C (entry 11). The results showed some temperature dependence, and the optimum temperature was 100 °C. Therefore, it is reasonable that the yield decreased drastically for CH_3CN because of its lower boiling point of 82 °C (entry 3). The time-dependence was also studied, and the results are shown in entries 5, 12, and 13. When the reaction time was changed from 24 h (entry 5) to 22 h and 20 h (entries 12 and 13), the yield decreased by approximately 10%. This shows that the reaction requires 24 h to achieve yields higher than 90% under the conditions used in this study.

In order to determine the scope of the **L1**-assisted Cu-catalyzed diaryl ether synthesis, various phenols and aryl halides were investigated under the optimized reaction conditions: 10 mol% CuI·**L1** in DMSO at 100 °C. As shown in entries 1 and 2 of Table 2, phenols with electron-donating substituents, *i.e.*, Me and MeO groups, afforded an approximately 90% yield in the coupling with 4-iodotoluene. Interestingly, 4-MeO and 2-MeO groups led to almost identical yields (entries 2 and 3). 2-Methylphenol gave the corresponding product in 75% yield (entry 4), which is 15% lower than that obtained with 4-methylphenol (entries 4 *vs.* 1), but 5% higher than that with phenol (entries 4 *vs.* 5). The results suggest that the steric hindrance of phenol can affect the reaction to some extent, but cannot be completely offset the electron-donating effect of the methyl group. Nearly identical results were obtained with the substrates featuring electron-withdrawing substituents, *i.e.*, 4- and

Table 2: Coupling of 4-iodotoluene with phenols in the presence of **L1**.[a]



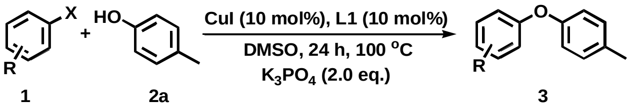
Entry	**2**	**3**	Yield (%)[b]
1			90
2			88
3			90
4			75
5			70
6			24
7			25
8			57
9			30

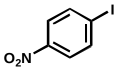
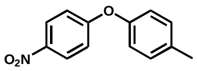
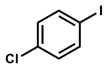
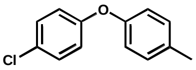
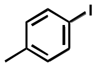
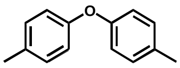
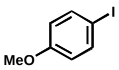
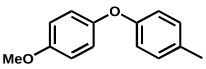
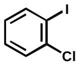
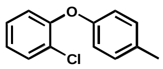
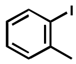
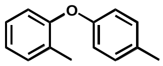
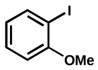
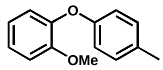
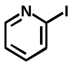
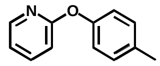
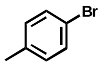
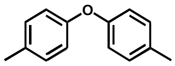
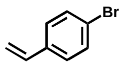
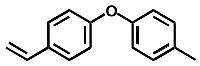
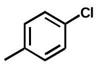
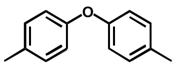
[a]General conditions: **1** (1 mmol), **2** (1.5 mmol), CuI (0.1 mmol), **L1** (0.1 mmol), K_3PO_4 (2 mmol), DMSO (7 mL), reaction time (24 h), and temperature (100 °C); [b]Isolated yield.

2-chlorophenols, with yields that were respectively ~25% (entries 6 and 7) and ~45% lower than that obtained using phenol, mostly due to the electronic effect. These results indicate that the electronic nature of the substituent is more influential for phenols than the steric hidrance (entries 1−7). The yield obtained with 3-hydroxypyridine was 57% (entry 8) lower than that obtained with phenol, which suggests that the pyridine ring lowers the nucleophilicity of the hydroxyl group than that of the phenyl ring. The yield of 2-methoxy-4-vinylphenol with 4-iodotoluene was only 30% (entry 9), which is 60% lower than that of the reaction involving 2-methoxyphenol (entries 9 *vs.* 3). Thus, the vinyl group clearly acts as an electron-withdrawing group.

The study of the scope of aryl halides is summarized in Table 3. Aryl iodides possessing 4-NO_2 and 4-Cl groups provided the corresponding products in 89% and 88% yields, respectively (entries 1 and 2), whereas 4-Me- and 4-MeO-substituted aryl iodides gave the corresponding products in 90% and 66% yields, respectively (entries 3 and 4). These results suggest that the reaction is not significantly affected by the electronic properties of the substituents at the *para* position, although the strongly electron-donating MeO group may lower the reactivity. On the other hand, *ortho*-substituted aryl iodides afforded the corresponding products in poor yields while the electronic nature of the substituents, Cl, Me or MeO, had slightly influenced the results, affording the similar yields of lower than 30% (entries 5−7). Therefore, steric hindrance can be considered to be a highly influential factor, in contrast with the results for phenols (Table 2). 2-Iodopyridine gave the corresponding product in an excellent yield of 95% (Table 3, entry 8). The result shows that the electronegativity of the N atom facilitates high reactivity, which suggests that the reaction system is useful for the *O*-arylation of various nitrogen-containing aromatic compounds.

Table 3: Coupling of aryl halides with *p*-cresol in the presence of **L1**.[a]



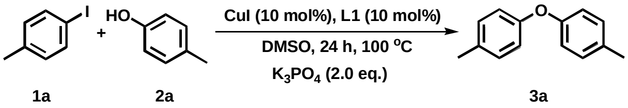
Entry	**1**	**3**	Yield (%)[b]
1			89
2			88
3			90
4			66
5			28
6			23
7			20
8			95
9			13
10			13[c]
11			0

[a]General conditions: **1** (1 mmol), **2** (1.5 mmol), CuI (0.1 mmol), **L1** (0.1 mmol), K_3PO_4 (2 mmol), DMSO (7 mL), reaction time (24 h), and temperature (100 °C); [b]Isolated yield; [c]The yield of oligomers was ~15% yield in this experimental run.

Less-reactive aryl bromides and 4-chlorotoluene were investigated under the optimum conditions. 4-Bromotoluene gave the corresponding product in only 13% yield, and lesser-reactive 4-chlorotoluene did not give any product (entry 11). On the other hand, 4-bromostyrene afforded the same yield with 4-bromotoluene in spite of the electron-withdrawing vinyl group (entries 9 and 10) and a small amount of oligomeric products was obtained in 5–15% yield (M_n = 780), as shown in entry 10 and Figure S3 (Supporting Information File 4). We believe that the low reactivity of the substrate facilitated this side reaction, which mechanism seems to be similar to that of atom transfer radical polymerization [46].

For the Cu-assisted *O*-arylation reaction, some radical mechanisms have been proposed by several researchers [34] such as Jenkins and Kochi [47,48], van Koten *et al*. [49] In order to examine the possibility of radical species formation and their effects, free radical scavengers, cumene and 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), also known as a living radical polymerization mediator [50], were applied to the present reaction system (Table 4) [51,52]. When 1 mmol of cumene, *i.e.*, the same amount of aryl iodide and 10 times more than the amount of CuI, was added, the yield decreased from 90% (entry 2) to 46%, as shown in entry 3 of Table 4. This

Table 4: Effect of free radical scavengers on the coupling reaction of 4-iodotoluene with *p*-cresol.[a]



Entry	Ligand	Additive	Yield(%)[b]
1	–	–	55
2	**L1**	–	90
3	**L1**	Cumene	46
4	**L1**	TEMPO	32
5	**L1**	TEMPO[c]	28

[a]General conditions: **1a** (1 mmol), **2a** (1.5 mmol), CuI (0.1 mmol), **L1** (0.1 mmol), additive (1 mmol), K_3PO_4 (2 mmol), DMSO (7 mL), reaction time (24 h), and temperature (100 °C); [b]Isolated yield. [c]3 mmol.

yield is about 10% lower than that of the reaction without any ligand (entries 3 *vs.* 1), and it suggests that radical intermediates can be involved in the reaction. The same amount of TEMPO (1 mmol) was examined and a lower 32% yield was obtained (entry 4). This yield is about 60% of that under the original conditions, however, TEMPO could also react with aryl halide directly as it is a radical species. While 3.0 mmol of TEMPO further lowered the yield (28%, entry 5), it could not completely quench the reaction. Therefore, although some radical species can be generated, its amount seems to be small considering that the amount of the radical scavengers used are 10 to 30 times the catalyst in the present reaction system.

Based on the previous studies on the mechanism [25,53] and the current results for DMSO, a possible mechanism for the **L1**-promoted CuI-catalyzed coupling reaction of phenols with aryl iodides is presented in Figure 5. The generalized mechanism involves oxidative addition (**OA**) of Cu(I) to an aryl halide to form the Cu(III) intermediate 2, anion exchange or nucleophilic substitution (**NS**) by a phenoxide, and reductive elimination (**RE**) to produce a diaryl ether and regenerate the Cu(I) catalyst [52]. In this process, the mixed ligand, **L1**, also exhibits different behavior from that of **L8** featuring only pyridine moieties; in other words, N_{py} and N_{pz} in **L1** play different roles while working cooperatively: N_{py} favors the electron-rich copper center and promotes the coordination of the aryl iodide, N_{pz} is weaker and accelerates the **NS** and **RE** steps, which begin from the electrophilic Cu(III)-centered complex [25]. In addition, this mechanism corresponds to the observation that the steric effect of the substituent is more influential, especially at the *ortho*-position, for aryl halides than for phenols, because the aromatic group of the former binds directly to the copper atom in the intermediate **2** while phenols form the Cu-O bond in the intermediate **3** so that the substituents are away from the reaction center.

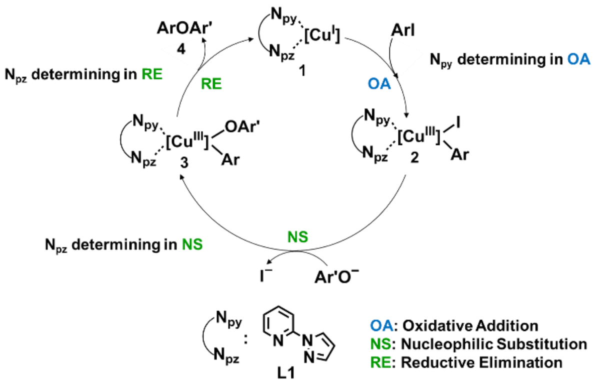


Figure 5: Possible mechanism for CuI·**L1**–catalyzed coupling of phenols with aryl iodides.

Conclusion

Three pyrazole-containing N$_2$- and N$_3$-ligands (**L1**–**L3**) and four N$_2$- and N$_3$-ligands (**L4**–**L7**) featuring only pyridine moieties were used for the CuI-catalyzed coupling of aryl halides with phenols. **L1** bearing a weakly electron-donating N$_{pz}$ atom and a strongly electron-donating N$_{py}$ atom was more effective than **L8** bearing two N$_{py}$ binding sites, and caused a 50% reduction in the catalyst loading from 20 mol% CuI·**L8** [30] (CuI/**L8** in 1:2 ratio) to 10 mol% CuI·**L1** (CuI/**L1** in 1:1 ratio) while consistently affording yields of up to 90% at 100 °C in DMSO. The electronic nature of the substituent and steric hindrance exhibited different effects on the phenols and aryl halides. Based on the results, a rationalized non-radical mechanism was presented to explain the opposite effects of the substituent on phenols and aryl halides as well as the good performance of unsymmetrical ligand **L1**.

Experimental

X-ray diffraction measurement

Single crystals suitable for X-ray diffraction analysis were prepared from the saturated acetonitrile solutions of the complexes. Crystallographic information files for [CuI**L1**]$_2$ and CuBr**L6** have been deposited with the Cambridge Structural Database. CCDC 1884812 and 1884813 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures. The detailed crystallographic data is summarized in Table S1.

General procedure for synthesis of CuI-catalyzed diaryl ether

A 30 mL Schlenk flask equipped with a Teflon-coated magnetic stirring bar was evacuated and backfilled with nitrogen; this sequence was repeated three times. The equipment was then charged with CuI (19.0 mg, 0.1 mmol), ligand (0.1 mmol), K_3PO_4 (424.5 mg, 2.0 mmol), aryl halide (1.0 mmol), and phenol (1.5 mmol) in DMSO (7.0 mL), and the resulting solution was stirred at 100 °C for 24 h. After allowing the flask to cool to room temperature, the mixture was diluted with 20 mL ethyl acetate and filtered. The filter cake was washed thrice with10 mL ethyl acetate and filtered. The filtrate was collected and washed with distilled water (3 × 20 mL). The organic layer was collected, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified using preparative thin layer chromatography (silica gel, hexane : ethyl acetate = 50:1 unless otherwise specified) to afford the corresponding diaryl ether product. (see Supporting Information File 2 for full experimental data)

Supporting Information

Supporting Information File 1: CIF file of [CuI·**L1**]$_2$ (the dimeric form of CuI·**L1**)

Supporting Information File 2: CIF file of CuBr·**L6**

Supporting Information File 3: Crystallographic Data

Supporting Information File 4: Materials, experimental procedures and data, references, spectroscopic data

ORCID® iDs

Koich Kodama - 0000-0002-8567-9360

Takuji Hirose - 0000-0003-4121-0963

References

1. Frlan, R.; Kikelj, D. *Synthesis* **2006**, *14*, 2271–2285. doi:10.1055/s-2006-942440

2. Bistri, O.; Correa, A.; Bolm, C. *Angew. Chem., Int. Ed.* **2008**, *47*, 586–588. doi:10.1002/anie.200704018

3. Theil, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 2345–2347. doi:10.1002/(SICI)1521-3773(19990816)38:16<2345::AID-ANIE2345>3.0.CO;2-5

4. Eicher, T.; Fey, S.; Puhl, W.; Büchel, E.; Speicher, A. *Eur. J. Org. Chem.* **1998**, *26*, 877–888. doi:10.1002/(SICI)1099-0690(199805)1998:5<877::AID-EJOC877>3.0.CO;2-S

5. Iyoda, M.; Sakaitani, M.; Otsuka, H.; Oda, M. *Tetrahedron Lett.* **1985**, *26*, 4777–4780. doi:10.1016/S0040-4039(00)94949-9

6. Zhu, J. *Synlett* **1997**, *2*, 133–144. doi:10.1055/s-1997-722

7. Boger, D. L.; Patane, M. A.; Zhou, J. *J. Am. Chem. Soc.* **1994**, *116*, 8544–8556. doi: 10.1021/ja00098a015.

8. Eicher, T.; Walter, M. *Synthesis* **1991**, 469–473. doi:10.1055/s-1991-26496

9. Deng, H.; Jung, J.–K.; Liu, T.; Kuntz, K.W.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2003**, *125*, 9032–9034. doi:10.1021/ja030249r

10. Ullmann, F. *Ber. Dtsch. Chem. Ges.* **1904**, *37*, 853–854. doi:10.1002/cber.190403701141

11. Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691–1692. doi:10.1002/cber.19060390298

12. Lindley, J. *Tetrahedron* **1984**, *40*, 1433–1456. doi:10.1016/S0040-4020(01)91791-0

13. Mann, G.; Incarvito, C.; Rheingold, A. L.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 3224–3225. doi:10.1021/ja984321a

14. Zhang, Y.; Ni, G.; Li, C.; Xu, S.; Zhang, Z.; Xie, X. *Tetrahedron*, **2015**, *71*, 4927–4932. doi:10.1016/j.tet.2015.05.104

15. Burgos, C. H.; Barder, T. E.; Huang, X.; Buchwald, S. L. *Angew. Chem.* **2006**, *118*, 4427–4432. doi:10.1002/ange.200601253

16. Liu, Y.; Park, S. K.; Xiao, Y.; Chae, J. *Org. Biomol. Chem.* **2014**, *12*, 4747–4753. doi:10.1039/C4OB00649F

17. Beletskaya, I. P.; Cheprakov, A. V. *Coordin. Chem. Rev.* **2004**, *248*, 2337–2364. doi:10.1016/j.ccr.2004.09.014

18. Zhang, Q.; Wang, D.; Wang, X.; Ding, K. *J. Org. Chem.* **2009**, *74*, 7187–7190. doi:10.1021/jo9012157

19. Wong, K. T.; Ku, S. Y.; Yen, F. W. *Tetrahedron Lett.* **2007**, *48*, 5051–5054. doi:10.1016/j.tetlet.2007.05.094

20. Mino, T.; Yagishita, F.; Shibuya, M.; Kajiwara, K.; Shindo, H.; Sakamoto, M.; Fujita, T. *Synlett* **2009**, *15*, 2457–2460. doi:10.1055/s-0029-1217822

21. Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131. doi:10.1021/cr8002505

22. Liu, Y. H.; Li, G.; Yang, L. M. *Tetrahedron Lett.* **2009**, *50*, 343–346. doi:10.1016/j.tetlet.2008.11.005

23. Cheng, A.-Y.; Hsieh, J.-C. *Tetrahedron Lett.* **2012**, *53*, 71–75. doi:10.1016/j.tetlet.2011.10.149

24. Niu, J.; Zhou, H.; Li, Z.; Xu, J.; Hu, S. *J. Org. Chem.* **2008**, *73*, 7814–7817. doi:10.1021/jo801002c

25. Ouali, A.; Spindler, J. F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906–1916. doi:10.1002/adsc.200600628

26. Lipshutz, B. H.; Unger, J. B.; Taft, B. R. *Org. Lett.* **2007**, *9*, 1089–1092. doi:10.1021/ol0700409

27. Hosseinzadeh, R.; Tajbakhsh, M.; Mohadjerani, M.; Alikarami, M. *Synlett* **2005**, *7*, 1101–1104. doi:10.1055/s-2005-865198

28. Cristau, H. J.; Cellier, P. P.; Hamada, S.; Spindler, J. F.; Taillefer, M. *Org. Lett.* **2004**, *6*, 913–916. doi:10.1021/ol036290g

29. Ouali, A.; Spindler, J. F.; Cristau, H. J.; Taillefer, M. *Adv. Synth. Catal.* **2006**, *348*, 499–505. doi:10.1002/adsc.200505385

30. Zhao, Y.; Wang, X.; Kodama, K.; Hirose, T. *ChemistrySelect*, **2018**, *3*, 12620–12624. doi:10.1002/slct.201802278

31. Ojwach, S. O.; Darkwa, J. *Inorg. Chim. Acta.* **2010**, *363*, 1947–1964. doi: 10.1016/j.ica.2010.02.014.

32. Das, T.; Chakraborty, A.; Sarkar, A. *Tetrahedron Lett.* **2014**, *55*, 7198–7202. doi:10.1016/j.tetlet.2014.11.009

33. Jameson, D. L. *J. Org. Chem.* **1990**, *55*, 4992–4994. doi:10.1021/jo00304a007.

34. Sambiagio, C.; Marsden, S. P.; Blacker, A. J.; McGowan, P. C. *Chem. Soc. Rev.* **2014**, *43*, 3525–3550. doi:10.1039/C3CS60289C

35. Zhu, D.; Wang, R.; Mao, J.; Xu, L.; Wu, F.; Wan, B. *J. Mol Catal. A-Chem.* **2006**, *256*, 256–260. doi:10.1016/j.molcata.2006.05.005

36. Woods, B. P.; Orlandi, M.; Huang, C.-Y.; Sigman, M. S.; Doyle, A. G. *J. Am. Chem. Soc.* **2017**, *139*, 5688–5691. doi:10.1021/jacs.7b03448

37. Niesel, J.; Pinto, A.; N'Dongo, H. W. P.; Merz, K.; Ott, I.; Gust, R.; Schatzschneider, U. *Chem. Commun.* **2008**, 1798–1800. doi:10.1039/B719075A

38. Kovács, A.; Varga, Z. *Coord. Chem. Rev.* **2006**, *250*, 710–727. doi:10.1016/j.ccr.2005.04.031

39. Wehman, P.; Kaasjager, V. E.; de Lange, W. G. J.; Hartl, F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3751–3761. doi:10.1021/om00008a024

40. Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954–6971. doi:10.1002/anie.200804497

41. Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, *1*, 326–330. doi:10.1039/C0SC00245C

42. Ma, Z.; Zaera, F. *J. Phys. Chem. B* **2005**, *109*, 406–414. doi:10.1021/jp046017b

43. Zhang, S.; Zhu, Z.; Ding, Y. *Dalton Trans.* **2012**, *41*, 13832–13840. doi:10.1039/C2DT31500A

44. de la Hoz, A.; Díaz-Ortiz, Á.; Moreno, A. *Chem. Soc. Rev.* **2005**, *34*, 164–178. doi:10.1039/B411438H

45. Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78–88. doi:10.1021/ja0781893

46. Matyjaszewski, K. *Macromolecules* **2012**, *45*, 4015–4039. doi:10.1021/ma3001719

47. Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 843–855. doi:10.1021/ja00758a024

48. Jenkins, C. L.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 856–865. doi:10.1021/ja00758a025

49. Aalten, H. L.; van Koten, G. Grove, D. M.; Kuilman, T.; Piekstra, O. G.; Hulshof, L. A.; Sheldon, R. A. *Tetrahedron* **1989**, *45*, 5565–5578. doi:10.1016/S0040-4020(01)89502-8

50. Nicolas, J.; Guillaneuf, Y.; Lefay, C.; Bertin, D.; Gigmes, D.; Charleux, B. *Prog. Polym. Sci.* **2013**, *38*, 63–235. doi:10.1016/j.progpolymsci.2012.06.002

51. Rahman, M. T.; Deschamps, J. R.; Imler, G. H.; Schwabacher, A. W.; Cook, J. M. *Org. Lett.* **2016**, *18*, 4174–4177. doi:10.1021/acs.orglett.6b01526

52. Huang, W.-K.; Chen, W.-T.; Hsu, I.-J.; Han, C.-C.; Shyu, S.-G. *RSC Adv.* **2017**, *7*, 4912–4920. doi:10.1039/C6RA27757H

53. Cohen, T.; Wood, J.; Dietz Jr., A. G. *Tetrahedron Lett.* **1974**, 3555–3558. doi:10.1016/S0040-4039(01)91965-3