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β-Ketoimine as an efficient ligand for copper-catalyzed N-arylation of nitrogen-containing heterocycles with aryl halides

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ABSTRACT

An efficient copper catalyst system, Cu_2O/β-ketoimine L_1, for the N-arylation of nitrogen-containing heterocycles with aryl iodides and bromides has been developed. The system works well with the electron-rich, -neutral, and -deficient aryl bromides to afford the products in good to excellent yields.

The Ullmann-type coupling reactions are one of the most powerful approaches for the formations of *N*-Arylazoles (*N*-arylimidazoles, *N*-arylpyrroles, *N*-arylindoles, etc.) which are the structural motif found in many biologically active natural products and pharmaceutically interesting compounds.[1] The traditional copper-catalyzed Ullmann coupling reactions were conducted under harsh conditions, including high temperature, stoichiometric amount of copper agent, and extended periods of time. Moreover, the method has the drawback of low functional group tolerance and poor substrate generality.[2] Since Buchwald[3] and Taillefer[4] reported, respectively, that copper-based coupling reaction of nitrogen-containing heterocycles with aryl halides could be improved with an addition of diamines and oxime/imine derivatives as additives, exhaustive efforts have been paid to exploring efficient ligands. Indeed, various compounds have been found to be efficient as ligands for these coupling reactions, including amino acids, diamines, diimines, aminoarenethiol, oxime-phosphine, 8-hydroxyquinoline, 1,10-phenanthrolines, etc.[5] However, the majority of the reactions are limited to the coupling of imidazoles with aryl iodides or of heteroarylamines possessing strongly electron-donating groups or aryl halides with strongly electron-withdrawing groups or of unhindered substrates.

Only very recently have significant advances been achieved for the copper-catalyzed coupling reactions of imidazoles with aryl bromides or of hindered substrates or of functional substrates by use of the new ligands explored, such as 4,7-dimethoxy-1,10-phenanthrolines,[6] (*s*) pyrrolidinylmethylmidazoles,[7] *N*,*N*′-dimethylethylenediamine,[8] 2-aminopyrimidine-4,6-diol,[9] and β-keto esters.[10] Therefore, the further discovery of new facile ligand structures for the copper-catalyzed cross-coupling reactions of imidazoles with aryl halides is still an area of considerable interest. Here we report the efficient use of β-ketoimine for the copper catalyzed N-arylation of imidazoles with aryl bromides bearing electron-donating groups (see Scheme 1).

The ligands L_1–L_7 were synthesized by known literature methods (Fig. 1)[11] Reaction of iodobenzene with imidazole was conducted with varied copper salt, ligand, base and solvent in order to find the optimum conditions. The results are listed in Table 1.[12] No desired coupling product was obtained without the presence of copper salt and ligand. It was notable that the reaction with Cu_2O catalyst and KO^tBu as the base could afford the coupling product in 47% yield at 60 °C after 24 h without ligand (Table 1, entry 2).[13] Upon addition of a ligand, however, the remarkable

$$\text{Ar-X} \quad + \quad \text{Het-NH} \xrightarrow[\text{t-BuOK, DMF, 45-130 }^{o}\text{C}]{Cu_2O\text{(5-10\%)}, L_1\text{(10-20\%)}} \text{Ar-N-Het}$$

X=I,Br
Ar=Aryl
Het-NH=*N*-Heterocycle

Scheme 1.

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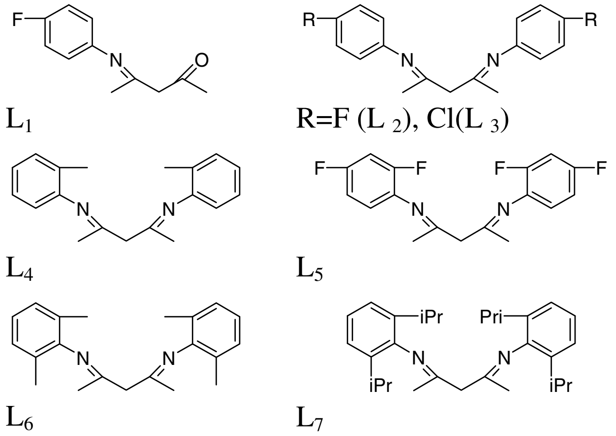


Figure 1. Ligands for copper-catalyzed N-arylation of imidazoles.

increase in reactivity was observed (Table 1, entries 6 and 14–19). Among the ligands L_1–L_7 tested, L_1 is the most efficient, while steric hindered β-diketiimine L_7 and β-diketiimine with strong electron-withdrawing groups L_5 are less efficient. For example, the reaction with L_1 afforded the coupling product in 90% yield using 5 mol % Cu_2O at 60 °C after 24 h while only 53% and 60% yields were obtained for the same reaction with L_5 and L_7, respectively (Table 1, entries 6, 17, and 19). The catalytic activity of cuprous salts was compared and Cu_2O was found to be the most efficient. The de-

Table 1
Effect of ligand, base, solvent,and copper salt on the coupling of imidazole with iodobenzene[a]

Entry	L_x	Copper salt	Base	Solvent	Yield[b] (%)
1	—	—	*t*-BuOK	DMF	NR[c]
2	—	Cu_2O	*t*-BuOK	DMF	47
3	L_1	CuBr	*t*-BuOK	DMF	63
4	L_1	CuCl	*t*-BuOK	DMF	7
5	L_1	CuI	*t*-BuOK	DMF	75
6	L_1	Cu_2O	*t*-BuOK	DMF	90
7	L_1	Cu_2O	$CsCO_3$	DMF	65
8	L_1	Cu_2O	K_3PO_4	DMF	58
9	L_1	Cu_2O	K_2CO_3	DMF	45
10	L_1	Cu_2O	Na_2CO_3	DMF	NR[c]
11	L_1	Cu_2O	*t*-BuOK	DMSO	70
12	L_1	Cu_2O	*t*-BuOK	TOL	NR[c]
13	L_1	Cu_2O	*t*-BuOK	CH_3CN	<5
14	L_2	Cu_2O	*t*-BuOK	DMF	80
15	L_3	Cu_2O	*t*-BuOK	DMF	76
16	L_4	Cu_2O	*t*-BuOK	DMF	67
17	L_5	Cu_2O	*t*-BuOK	DMF	53
18	L_6	Cu_2O	*t*-BuOK	DMF	78
19	L_7	Cu_2O	*t*-BuOK	DMF	60
20	L_1	Cu_2O	*t*-BuOK	DMF	100[d]
21	L_1	Cu_2O	*t*-BuOK	DMF	84[e]

[a] Reaction conditions: iodobenzene (1 mmol), imidazole (1.2 mmol), Cu_2O (0.05 mmol), ligand (0.1 mmol),base (2 mmol) and DMF (1 ml) under Ar atmosphere at 60 °C for 24 h.

[b] Isolated yields.

[c] No reaction.

[d] At 80 °C.

[e] Cu_2O (0.1 mmol), L_1 (0.2 mmol) at 45 °C.

Table 2
Catalytic N-arylation of diazoles with aryl halides by Cu_2O[a]

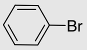
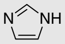
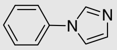
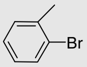
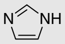
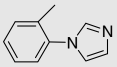
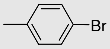
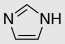
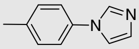
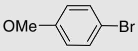
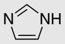
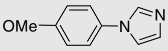
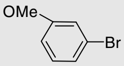
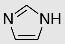
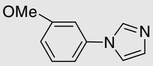
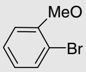
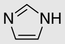
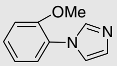
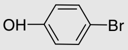
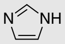
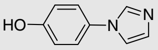
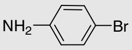
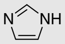
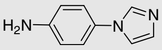
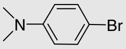
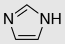
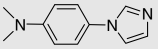
Entry	Aryl halide	Diazole	Product	Temperature (°C)	Yield[b] (%)
1				110	90
2				130	92
3				130	99
4				130	92
5				130	91
6				130	73
7				130	95
8				130	85
9				130	98

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Table 2 (*continued*)

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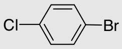
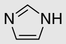
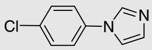
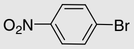
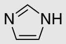
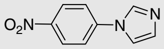
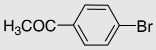
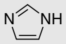
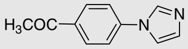
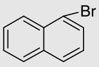
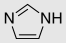
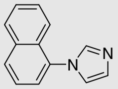
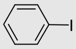
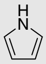
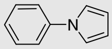
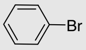
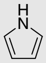
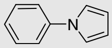
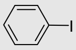
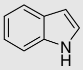
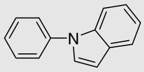
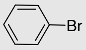
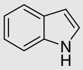
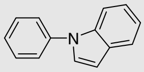
10				130	95
11				130	53/70[d]
12				130	57/73[d]
13				130	92
14				80	96[c]
15				110	82
16				110	95[c]
17				130	45

[a] Reaction conditions: aryl halide (1.0 mmol), Het-NH (1.2 mmol), KO^tBu (2.0 mmol) in the presence of L_1 (20 mmol %) and Cu_2O (10 mmol %) in 1.0 ml of DMF under Ar atmosphere for 24 h.

[b] Isolated yields.

[c] Cu_2O (0.05 mmol), L_1 (0.1 mmol).

[d] Cs_2CO_3 (2 mmol) instead of KO^tBu.

crease in the order $Cu_2O > CuI > CuBr > CuCl$ was observed (Table 1, entries 3–6). Base influenced the progress of the reaction greatly. The highest yield was obtained when KO^tBu was used (Table 1, entries 6–10). Of the solvents investigated, DMF was found to be the most effective, whereas CH_3CN and toluene were ineffective (Table 1, entries 12 and 13). It was notable that the reaction could be conducted at temperatures as low as 45 °C with 10 mol % Cu_2O and KO^tBu in DMF to give the product in 84% yield (Table 1, entry 21).

The arylation of imidazole with various aryl bromides and of N-containing heterocycles with aryl halides was further examined under the optimum conditions to evaluate the scope and the generality of Cu_2O/L_1 system.

The reaction of imidazole with electron-rich, -neutral, and -deficient aryl bromides was first tested, since substrates which contain certain functional groups have proven to be problematic in the arylation of imidazoles. The results are collected in Table 2. As shown in Table 2, the reactions with these aryl bromides proceeded smoothly with 10 mol % Cu_2O to provide the corresponding coupling products in good to excellent yields. Notably, the present catalyst system could facilitate the arylation of imidazole with *ortho*-substituted aryl bromides. For example, the reaction of imidazole with 2-methyl bromobenzene and 2-methoxybromobenzene afforded the corresponding coupling products in 92% and 73% yields at 130 °C (Table 2, entries 2 and 6). Generally, the Ullmann-type condensations are sensitive to steric hindrance near the halogen atom, and only a few examples concerning with the Cu-catalyzed arylation of imidazole with hindered aryl halides were found in the literatures.[6] The reaction with 4-$NO_2C_6H_4Br$ and 4-$CH_3COC_6H_4Br$ afforded the corresponding product in moderate yields, 53% and 57%. The yields can be improved to 70% and 73%, respectively, when $CsCO_3$ was used, instead of KO^tBu as the base (Table 2, entries 11 and 12).

Arylation of other N-containing heterocycles with aryl halides was then examined (Table 2). The present catalyst system was found to be efficient for the arylation of pyrrole with iodobenzene at 80 °C to afford the product in 96% yield after 24 h, even the amount of Cu_2O decreased to 5 mol % (Table 2, entry 14). Furthermore, the catalyst system could also be applied in the reaction of indole with iodobenzene. The corresponding product in high yield (95%) was obtained at 110 °C with the same amount of Cu_2O (Table 2, entry 16). It was expected that the same two reactions with bromobenzene were relatively difficult. To obtain the coupling product in good yield (82%) for the reaction of pyrrole with bromobenzene, the amount of Cu_2O needs to increase to 10 mol % and the reaction temperature should raise to 110 °C related to that with iodobenzene (Table 2, entry 15). The arylation of indole with bromobenzene afforded the product in moderate yield, even the reaction temperature increased to 130 °C (Table 2, entry 17).

In summary, β-ketoimine was found to be an efficient, inexpensive, and facile ligand for the Cu_2O-catalyzed N-arylation of imidazoles with aryl iodides and bromides. Particularly, the system works well with the electron-rich, -neutral, and -deficient aryl bromides. The further study on design and application of new ligands in copper based Ullmann-type coupling reaction is currently ongoing.

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References and notes

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11. (a) Scheibe, G. *Chem. Ber.* **1923**, *56*, 1923; (b) Budzelaar, P. H. M.; Oort, B. VA.; Orpenb, A. G. *Eur. J. Inorg. Chem.* **1998**, 1485; (c) *Synthetic procedure and characterization data for* L_1. A mixture of acetylacetone (25.75 ml, 0.25 mol), 4-fluoroaniline (24.0 ml, 0.25 mol), and (5 mmol) toluene-4-sulfonic acid was refluxed for 4 h in toluene, and the water was removed. The reaction mixture was filtered through a plug of silica gel and concentrated to dry in vacuo. The residue was dissolved in refluxing hexane and then cooled for crystallization. Ligand L_1 was obtained as colorless crystals. (33.8 g, 70% yield). ^1H NMR (300 MHz, $CDCl_3$): δ 1.91 (s, 3H), 2.08 (s, 3H), 5.18 (s, 1H), 7.00–706 (m, 4H), 12.33 (s, 1H) ppm. ^{13}C NMR: δ 19.6, 29.1, 97.4, 115.7, 116.0, 126.7, 126.8, 134.6, 135.0, 158.9, 160.4, 162.1, 196.2 ppm. HRMS *m/z*: 193.0910 (193.0903 calcd. for $C_{11}H_{12}NOF$). Mp: 45.9–47.2C. °C.
12. A typical procedure for the arylation is as follows: To a solution of imidazole (1.2 mmol) and iodobenzene (1 mmol) in DMF (1 ml) under an argon atmosphere were added Cu_2O (7.2 mg, 5 mol %), L_1 (19.3 mg, 10 mol %), and KO^tBu (2 mmol, 224 mg)in turn under Ar atmosphere. The reaction mixture was stirred for 20 min at room temperature, and then heated to 60 °C for 24 h. The reaction mixture was then cooled to ambient temperature, diluted with 2–3 ml of ethyl acetate, filtered through a plug of silica gel, and washed with ethyl acetate (3×20 ml). The filtrate was concentrated and the resulting residue was purified by column chromatography on silica gel to provide the desired product (138 mg, 90% yield).
    1-Phenyl-1*H*-imidazole (Table 1).^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (s, 1H), 7.30 (s, 1H), 7.36–7.41 (m, 3H), 7.47–7.51 (m, 2H), 7.87 (s, 1H) ppm. ^{13}C NMR: δ 118.1, 121.3, 127.4, 129.8, 130.3, 135.4, 137.2 ppm. HRMS *m/z*: 144.0685 (144.0687 calcd. for $C_9H_8N_2$).
13. For the Cu-catalyzed coupling reaction under free ligand: (a) Elena, S.; de Vries Johannes, G.; Gerard van Kote *Tetrahedron Lett.* **2007**, *48*, 7366; (b) Xing, X. L.; Wu, J. L.; Feng, G. F.; Dai, W. L. *Tetrahedron* **2006**, *62*, 6774.