Facile CuI-Catalyzed Arylation of Azoles and Amides Using Simple Enaminones as Efficient Ligands

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Abstract: (*E*)-3-(Dimethylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one was found to be an excellent ligand for copper-catalyzed Narylation of azoles and amides with aryl halides under mild conditions. The reaction took place at 82 °C in MeCN with broad functional-group compatibility. A combination of the ligand and CuI proved to be an efficient catalytic system to promote the coupling reactions of aryl halides with azoles and amides.

Key words: copper, ligand, azoles, amides, arylation

Copper-catalyzed Ullmann reaction¹ and the related Goldberg reactions² are important methods for the formation of C-N bond. Traditional Ullmann-Goldberg reactions are generally conducted under harsh reaction conditions under stoichiometric amounts of copper reagents, high temperature, and with low tolerance of functional groups. During the past decade, Buchwald³ and Hartwig⁴ have made significant contribution in the palladium/phosphineligand-promoted cross-coupling reactions, which proceeded under considerably milder conditions to construct aryl C-N bond and other C-heteroatom bonds.5,6 However, its large-scale application for industry is difficult, because palladium catalysts are expensive and phosphine ligands are usually not easy to prepare, sensitive to air or moisture, and toxic. As an alternative metal-catalyzed protocol, copper-catalyzed coupling reactions⁷ attract greater attention because of the low cost of copper reagents. Representatively, Buchwald⁸ and Ma,^{9,10a-c} respectively, accomplished the same transformation by combining copper(I) iodide with salicylic amide derivatives and proline. Thereafter, a number of efficient ligands with N-N,^{10d,h} N-O,^{9c,10d,g} O-O,^{8b,i,10d} N-S,^{10a-c,e} and N-P¹¹ coordination sites that could form stable chelates with copper were discovered. Recently, Hu12 and You13 reported the copper-catalyzed N-arylation of nitrogen-containing heterocycles under ligand-free and mild conditions. However, only aryl iodides were successfully applied in their reactions. Neither aryl bromides nor other N-containing substrates were reported as proper partners in their ligand-free systems. Therefore, exploring new ligands with broad application scope still plays an important role in the Ullmann–Goldberg coupling reactions.^{7,9c,10,11} We previously reported the 1,1-diamide motif as an efficient

SYNLETT 2009, No. 16, pp 2663–2668 Advanced online publication: 04.09.2009 DOI: 10.1055/s-0029-1217958; Art ID: W09109ST © Georg Thieme Verlag Stuttgart · New York ligand¹⁴ in Ullmann reactions. In this paper, based on the rationale given in Buchwald's first report of phenolic ligands,^{8b} we wish to report herein the use of a new phenolic-type ligand (*E*)-3-(dimethylamino)-1-(2-hydroxy-phenyl)prop-2-en-1-one in the efficient CuI-catalyzed N-arylation of both azoles and amides with a variety of aryl halides.



Figure 1 The ligands screened for C–N coupling

Initially, we synthesized a series of analogous enaminone compounds with N–O coordinate sites as candidate ligands (Figure 1). To select the most efficient ligand, the coupling reaction of iodobenzene with imidazole was chosen as the model reaction, and this reaction was carried out at 110 °C in the presence of 10 mol% of CuI, 20 mol% of ligand, and 2 equivalents of Cs_2CO_3 in DMSO under N_2 atmosphere for 12 hours.

Most of the ligand with N–O coordinate sites could promote the coupling reaction efficiently except L9 and L10, which yielded the desired products in less than 5% yield (Scheme 1). After analyzing the results from all entries in this section, we found that ligand L5 was the best among



Scheme 1 Ligand performances in the CuI-catalyzed N-arylation of imidazole

Table 1 N-Arylation of Imidazole under Different Conditions^a

)	Cul, L5		
1a 2a				
Entry	Solvent, base	CuI, ligand (mol%)	Temp (°C)	Yield (%) ^b
1	DMSO, Cs ₂ CO ₃	10, 20	110	76
2	DMSO, Cs ₂ CO ₃	10, 10	110	35
3	DMSO, Cs ₂ CO ₃	5, 10	110	53
4	DMF, Cs ₂ CO ₃	10, 20	110	57
5	dioxane, Cs ₂ CO ₃	10, 20	110	42
6	MeCN, Cs ₂ CO ₃	10, 20	82	88
7	MeCN, K ₂ CO ₃	10, 20	82	63
8	MeCN, MeONa	10, 20	82	84
9	MeCN, K ₃ PO ₄	10, 20	82	55
10	MeCN, Cs ₂ CO ₃	10, 0	82	22

^a Reaction conditions: iodobenzene (0.5 mmol), imidazole (0.5 mmol), base (1.0 mmol) in the presence of L5 and CuI catalyst in solvent (2 mL) under N_2 atmosphere for 12 h. ^b Isolated yields.

the ligands tested, and the desired products N-phenylimidazole was isolated in 76% yields (Table 1, entry 1).

To determine the most suitable reaction conditions, different parameters such as the amounts of Cul/L5, solvent, and the nature of the base were optimized on the same reaction (Table 1). It was found that a smaller amount of CuI was inefficient for the reaction. Increasing the amount of ligand L5 from 10 mol% to 20 mol% in the presence of 10 mol% CuI afforded N-phenylimidazole in higher yield (entries 1 and 2). Without ligand L5,¹⁵ the yield was decreased greatly (entries 1 and 10). Among the tested solvents, MeCN gave the best results (entries 1, 4-6). Both MeONa and Cs₂CO₃ were efficient bases as compared with K₂CO₃ and K₃PO₄ (entries 7 and 9). However, Cs_2CO_3 gave the optimal yield (entries 6 and 8).

After optimization, the best reaction conditions were 10 mol% CuI, 20 mol% ligand, and 2.0 equivalents of Cs₂CO₃ in MeCN at 82 °C. Ullmann-type coupling reactions of various aryl halides with different azoles were conducted, and the results are summarized in Table 2. As expected, aryl iodides showed better reactivity than aryl bromides. The reaction of aryl bromides with azoles yielded the desired products only in moderate yields (entries 1–8, 13–16, and 24). Further studies disclosed that aryl chlorides bearing electron-withdrawing groups were reactive in this kind of conversion and different azoles could be effectively arylated (entries 17-21). Moreover, heterocyclic aryl bromides were compatible with the present procedure and satisfactory results were obtained (entries 22 and 23).

Table 2 CuI/L5-Catalyzed N-Arylation of Azoles with Different Aryl Halides^a

	HetNH	Cul (10 mol%), L5 (20 mol%)		
ArX + 1		Cs ₂ CO ₃ (2 equiv), MeCN 82 °C	HetiNAr 2	
Entry	ArX	Product		Yield (%) ^b
1	PhI (Br) 1a (1b)			88 (43) ^c
2	1a (1b)	2a		92 (45) ^c
3	1a (1b)			78 (42) ^c
4	1a (1b)	2c		73 (29) ^c
5	4-ClC ₆ H ₄ 1c (1d)	2d I (Br) N≈√N→	CI	84 (38) ^c
6	1c (1d)	2e	CI	79 (40) ^c
7	1c (1d)	2f	—CI	89 (52) ^c
8	1c (1d)	2g	—CI	63 (33) ^c

Table 2	CuI/L5-Catalyzed N-Arylation of Azoles with Differe	ent
Aryl Hali	es ^a (continued)	

ArX + 1	HetNH C:	(10 mol%), L5 (20 mol%) 5₂CO3 (2 equiv), MeCN 82 °C 2	
Entry	ArX	Product	Yield (%) ^b
9	4-BrC ₆ H ₄ I 1e	N - Br	83
10	1e	Zi NBr 2i	81
11	1e	2J	91
12	1e	2k	61
13	4-MeC ₆ H ₄ Br 1f	2l	43°
14	1f		39°
15	1f		51°
16	1f		34°
17	2-O ₂ N-4- F ₃ CC ₆ H ₃ Cl 1g	2p $N = N - CF_3$ O_2N	79
18	1g	2q O_2N CF_3	87
19	1g	$2r$ $V \rightarrow CF_3$ O_2N $2s$	88

 Table 2
 CuI/L5-Catalyzed N-Arylation of Azoles with Different Aryl Halides^a (continued)



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^a Reaction conditions: aryl halide (0.5 mmol), azole (0.5 mmol), CuI (0.05 mmol), Cs_2CO_3 (1.0 mmol) and **L5** (0.1 mmol) in MeCN (2 mL) at 82 °C under N₂ atmosphere for 12 h.

^b Isolated yields.

^c KI (0.5 mmol) was used.

Encouraged by the successful application of **L5** in Ullmann-type reaction, we further employed our catalyst to the Goldberg-type N-arylation of amides. We optimized the coupling conditions of iodobenzene with 2-pyrrolidone as shown in Table 3. The effects of solvent and base in the coupling reaction were investigated by using 10 mol% CuI and 20 mol% ligand **L5** (entries 1–4 and 6–8). It was found that the transformation led to as low as only 14% yield without using ligand (entry 5). In the presence of Cs₂CO₃ as a base, **L5** as a ligand, and MeCN as a sol-

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Table 3 N-Arylation of Amide under Different Conditions^a



^a Reaction conditions: iodobenzene (0.5 mmol), 2-pyrrolidone (0.5 mmol), CuI (0.05 mmol), base (1.0 mmol) and **L5** (0.1 mmol) in solvent (2 mL) under N_2 atmosphere for 12 h. ^b Isolated yields.

vent, the desired product *N*-phenyl-pyrrolidin-2-one was obtained in the highest yields (entry 1).

To probe the generality of the optimized conditions, the reactions of aryl halides and amides were investigated (Table 4). It was easily found that all of aryl iodides, aryl bromides, and activated aryl chlorides could perform this transformation successfully, but aryl iodides were more active and led to better yields than aryl bromides (entries 1–8, 12–16, and 18). Meanwhile, the reaction of *para*-substituted aryl bromides and iodides bearing electron-withdrawing substituent gave the corresponding products in excellent yields (entries 1, 3, and 5–8).

Additionally, we also tried N-arylation of azoles and amides with various aryl bromides under harsh conditions at 130 °C in DMSO in the presence of 10 mol% of CuI, 20 mol% of L5, and 2 equivalents of Cs_2CO_3 under N_2 atmosphere for 12 hours. However, the yields were similar to the same transformation at 82 °C in MeCN with adding 1 equivalent of KI.

In summary, we have developed a ligand (E)-3-(di-methylamino)-1-(2-hydroxyphenyl)prop-2-en-1-one for the efficient copper-catalyzed Ullmann-type N-arylation of azoles and Goldberg-type N-arylation of amides. By using MeCN as a solvent, various azoles and amides were arylated with a broad range of aryl halides compared with traditional strategies. This protocol bears advantages of mild conditions and wide application scope. Therefore, this approach provided a simple and useful supplement for known methods.

 $\label{eq:cull_to_call} \begin{array}{ll} \mbox{Table 4} & \mbox{Cull_t5-Catalyzed N-Arylation of Amides with Different Aryl Halides}^a \end{array}$



 Table 4
 CuI/L5-Catalyzed N-Arylation of Amides with Different

 Aryl Halides^a (continued)
 Continued



 Table 4
 CuI/L5-Catalyzed N-Arylation of Amides with Different Aryl Halides^a (continued)



 a Reaction conditions: aryl halides (0.5 mmol), amides (0.5 mmol), CuI (0.05 mmol), Cs_2CO_3 (1.0 mmol), and L5 (0.1 mmol) in MeCN (2 mL) at 82 $^\circ$ C under N_2 atmosphere for 12 h. b Isolated yields.

^c KI (0.5 mmol) was used.

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- (15) General Procedure All chemicals were obtained from commercial source and used without further purification. A stirred suspension of aryl halides (0.5 mmol), azoles or amides (0.5 mmol), CuI powder (0.05 mmol), Cs_2CO_3 (1.0 mmol), and L5 (0.1 mmol) in MeCN was refluxed for 12 h (monitored by TLC) under nitrogen. After the mixture was cooled to r.t., the MeCN was removed in vacuo. The solid was then extracted with EtOAc (3 × 10 mL), washed with H₂O (3 × 10 mL), and dried over Na₂SO₄. After the solvent was removed, the crude mixture was purified by silica gel column chromatography to provide the desired product.