8-Hydroxyquinolin-*N*-oxide-Promoted Copper-Catalyzed C–S Cross-Coupling of Thiols with Aryl Iodides

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Abstract: 8-Hydroxyquinolin-*N*-oxide was identified as a superior ligand for CuI-catalyzed C–S coupling reactions of aryl iodides with thiols to afford the corresponding thioethers in excellent yield. The method shows excellent chemoselectivity and high functional-group tolerance in both coupling partners.

Key words: C–S coupling reactions, copper, cross-coupling, 8-hydroxyquinolin-*N*-oxide, Ullmann reaction

Transition-metal-catalyzed C-S bond formation is a very important method in organic chemistry due to the importance of related compounds in biologically and pharmaceutically active molecules, as well as organic materials and intermediates.¹ During the development of this method, several transition metals such as palladium, copper, nickel, cobalt, iron, and indium have been reported for this purpose.²⁻⁷ Among them, the copper-catalyzed C-S crosscoupling reactions have gained much more attention in the past decades because copper is an inexpensive metal as compared to palladium and other late-transition metals. It is noteworthy that the ligand has played an important role in improving both the efficiencies and scope of the methodology. Recently, several classes of ligands, including phosphazene,^{3a} ethylene glycol,^{3b} neocuproine,^{3c} N-methylglycine,^{3d} oxime-phosphine oxide ligand,^{3e} tripod ligand,^{3f} benzotriazole,^{3g} 1,2-diaminocyclohexane,^{3h} βketoester,^{3i,j} L-proline,^{3k} BINAM,³¹ 1,2,3,4-tetrahydro-8hydroxyquinoline,^{3m} and catechol violet,³ⁿ have been found to accelerate copper-catalyzed C-S bond-forming reactions.

Recently, we developed a series of new ligands which could promote the copper-catalyzed C–N and C–O coupling reaction under relatively mild conditions (Figure 1).⁸ Encouraged by this success, we envisioned that our catalytic system might be used for the C–S coupling reaction by choosing a suitable ligand. In this paper, we report that 8-hydroxyquinolin-*N*-oxide (**L2**) serves as an effective ligand for the copper-catalyzed C–S bond-forming reactions.

4-Methyliodobenzene and thiophenol were selected as model substrates to evaluate the catalytic activity of sys-

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Figure 1 Structures of previous reported ligands

tems comprised of the designed ligands. The prototypical reaction conditions were 10 mol% of CuI, 20 mol% of the ligand, and 1.5 equivalents of Cs₂CO₃ in DMSO (without drying) at 80 °C (Table 1, entries 1–4). The results showed that the highest yield (94%, Table 1, entry 2) was obtained when L2 was employed as the ligand. The effect of solvent was also evaluated, and DMSO is the most favorable solvent for the catalytic reaction (Table 1, entries 2, 5, 6). Using L2 as the ligand and DMSO as the solvent, reactions employing other bases, including K₂CO₃, K₃PO₄, and NaOt-Bu, were explored. NaOt-Bu was not suitable as a base. Cs_2CO_3 performed as the best base. K_2CO_3 and K_3PO_4 gave good results, but were not as good as Cs_2CO_3 (Table 1, entries 2, 10–12). The copper sources were also found to have remarkable effects on the reaction. The results demonstrated that CuI was superior to the other copper sources (Table 1, entries 2 and 7-9). No reaction was observed without any copper source. The results of the preliminary exploratory investigations described above showed that the optimal conditions for the C-S coupling reaction of 4-methyliodobenzene and thiophenol involves the use of 10 mol% CuI, 20 mol% L1, and 2.0 equivalents Cs₂CO₃ in DMSO at 80 °C.

The scope of the CuI–L1 catalytic process was carried out under the optimized conditions, and the results are summarized in Table 2.⁹ As shown in Table 2, both electronrich and electron-deficient aryl iodides were observed to display similar reactivities. For example, reactions of aryl iodides with a methyl substituent and thiophenol took place in high yield (86–95%, Table 2, entries 1–3), while the reaction of aryl iodides with a nitro substituent completed in 89–94% yield (Table 2, entries 6–8). It is notable that the coupling proceeded well even with a sterically Table 1 Optimization of Conditions for the Copper-Catalyzed Coupling of p-Iodoanisole and Thiophenola

+	HS -	[CuX], ligand base (2.0 equiv) Ar, solvent, 24 h	S S			
1a	2a		3a			
Entry	Ligand	Base	Catalyst equivalent (mol%)	Copper source	Solvent	Yield (%) ^b
1	L1	Cs ₂ CO ₃	20	CuI	DMSO	56
2	L2	Cs ₂ CO ₃	20	CuI	DMSO	94
3	L3	Cs ₂ CO ₃	20	CuI	DMSO	85
4	L4	Cs ₂ CO ₃	20	CuI	DMSO	60
5	L2	Cs ₂ CO ₃	20	CuI	DMF	90
6	L2	Cs ₂ CO ₃	20	CuI	toluene	60
7	L2	Cs ₂ CO ₃	20	CuBr	DMSO	86
8	L2	Cs ₂ CO ₃	20	CuBr ₂	DMSO	70
9	L2	Cs ₂ CO ₃	20	CuAc	DMSO	68
10	L2	K ₂ CO ₃	20	CuI	DMSO	85
11	L2	K ₃ PO ₄	20	CuI	DMSO	93
12 ^c	L2	NaOt-Bu	20	CuI	DMSO	5
13°	L2	Cs ₂ CO ₃	20	CuI	DMSO	0
14 ^c	L2	K ₂ CO ₃	20	CuI	DMSO	0
15	-	Cs ₂ CO ₃	20	CuI	DMSO	28
16	L2	Cs ₂ CO ₃	30	CuI	DMSO	96
17	L2	Cs ₂ CO ₃	10	CuI	DMSO	30
18	L2	Cs ₂ CO ₃	0	CuI	DMSO	trace

^a Reaction conditions: **1a** (1.5 mmol), **2a** (1.0 mmol), [CuX] (10 mol%), ligand (20 mol%), base (2.0 mmol), solvent (1 mL), Ar, 80 °C, 24 h. ^b Isolated yield.

° Conditions: r.t.

hindered substitute such as methyl and nitro at the ortho position (Table 2, entries 2, 3, 6, and 10). A heteroaryl iodide (3-iodopyridine) also underwent coupling with an excellent yield of 92% (Table 2, entry 13). The coupling reaction is also very chemoselective when a variety of other potentially reactive groups were present in the substrate. For example, aryl iodides coupled with thiophenol without affecting chloro and bromo groups present in the aryl ring (Table 2, entries 4, 5, 12, and 14). Moreover, the reaction showed a high chemoselectivity to the thiols other than arylation on the amino group (Table 2, entry 11). Finally, we observed that the coupling of 1-iodo-4-methylbenzene with various thiols such as 2-bromo-, 2-methyl-4-methyl-, 4-methoxy-, 2-amino-, and 4-aminobenzenethiol underwent the reaction in 90-98% yield (Table 2, entries 15-20).

In summary, we have developed a simple, efficient, and general methodology for copper-catalyzed C–S coupling reactions of aryl iodides with thiols using inexpensive 8-hydroxyquinolin-*N*-oxide as an ideal ligand. This method shows excellent functional-group compatibility and high selectivity in the presence of multiple potentially reactive groups at moderate temperatures.

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 Table 2
 CuI-Catalyzed C–S Coupling Reaction of Aryl Iodides with Thiols^a

R ¹	+ HS R ² L2 Cs ₂ C Df	II (10 mol%) 2 (20 mol%) O ₃ (2.0 equiv) MSO, 80 °C	R ²	
Entry	Aryl iodide	Thiol	Product	Yield (%) ^b
1		HS	S S S S S S S S S S S S S S S S S S S	92
2	la	2a HS	3a	95
3	1b	2a HS	3b	86
4		HS 2a		90
5	ld _{Cl}	HS 2a	3d CI 3e	91
6		HS 2a		94
7		HS 2a		89
8	O_2N	HS 2a	O_2N S C S C S C S C S	95
9	MeO	HS 2a	MeO	90
10			3i NO ₂	92

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Table 2 CuI-Catalyzed C-S Coupling Reaction of Aryl Iodides with Thiols^a (continued)

$R^{1} \xrightarrow{\qquad \qquad } R^{2} \xrightarrow{\qquad \qquad } R^{2} \xrightarrow{\qquad \qquad } R^{2} \xrightarrow{\qquad \qquad } R^{2} \xrightarrow{\qquad \qquad } R^{1} \xrightarrow{\qquad \qquad } R^{1} \xrightarrow{\qquad \qquad } R^{1} \xrightarrow{\qquad \qquad } R^{1} \xrightarrow{\qquad \qquad } R^{2}$						
Entry	Aryl iodide	Thiol	Product	Yield (%) ^b		
11	NH ₂	HS	NH ₂	88		
	1k	2a	3k			
12	Br	HS	Br	96		
	11	2a	3l			
13				92		
	1m	2a	3m			
14	CI	HS	CI Br	88		
	1n	2a	3n			
15		Br	Br	93		
	1a	2b	30			
16		HS	S S	96		
	1a	2c	3p			
17		H5		98		
	1a	2d	3q			
18		OMe	OMe	95		
	1a	2e	3r			
19		HS NH2	NH2	90		
	1 a	2f	3s			
20		HS H ₂ N	H ₂ N	92		
	1a	2g	3t			

^a Reaction conditions: ArI (1.5 mmol), thiol (1.0 mmol), Cs₂CO₃ (2.0 mmol) CuI (0.10 mmol, 10 mol%), L5 (0.20 mmol, 20 mol%), DMSO (1.0 mL), 80 °C, argon.

^b Isolated yield.

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(9) General Experimental Procedure An argon-filled flask was charged with CuI (20 mg, 0.1 mmol, 10 mol%), L5 (32 mg, 0.2 mmol, 20 mol%), Cs₂CO₃ (652 mg, 2 mmol, and thiophenol (1 mmol). The aryl iodide (1.5 mmol) and DMSO (1 mL) were injected into the flask under argon atmosphere. The contents were then stirred at 80 °C for 24 h. After allowing the mixture to cool to r.t., the mixture was diluted with EtOAc (20 mL) and filtered. The filtrate was washed with H₂O (2 × 10 mL). The organic phase was dried with Na₂SO₄, filtered, and the solvent was removed under vacuum, and the residue was purified by chromatography on silica gel to give the desired aryl sulfide. Spectroscopic Data of the Representative Compounds: (2,4,6-Trimethylphenyl)phenyl Sulfide (3c)

¹HNMR (400 MHz, CDCl₃): δ = 7.19–7.15 (t, *J* = 7.60 Hz, 2 H), 7.07–7.01 (m, 3 H), 6.93–6.91 (d, *J* = 7.60 Hz, 2 H), 2.39 (s, 6 H), 2.32 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 143.7, 139.2, 138.4, 129.3, 128.8, 126.9, 125.5, 124.4, 21.7, 21.1.

3-Pyridyl Phenyl Sulfide (3m)

¹HNMR (400 MHz, CDCl₃): $\delta = 8.56-8.55$ (s, 1 H), 8.46-8.45 (q, J = 4.8 Hz, 1 H), 7.60–7.58 (d, J = 8.00 Hz, 1 H), 7.39–7.29 (m, 5 H), 7.22–7.19 (q, J = 4.80 Hz, 1 H). ¹³C NMR (125 MHz, CDCl₃): $\delta = 151.1$, 147.8, 137.9, 133.9, 133.6, 131.7, 129.5, 127.8, 123.9.

2-(4-Tolylsulfanyl)phenyl Bromide (30)

¹HNMR (400 MHz, CDCl₃): δ = 7.54–7.52 (d, J = 7.6 Hz, 1 H), 7.40–7.38 (d, J = 8.00 Hz, 2 H), 7.23–7.21 (d, J = 8.00 Hz, 1 H), 7.13–7.08 (m, 1 H), 7.00–6.96 (m, 1 H), 6.82–6.79 (dd, J = 7.60 Hz, 1 H), 2.38 (s, 3 H). ¹³C NMR (125 MHz, CDCl₃): δ = 139.8, 139.0, 134.4, 132.9, 130.5, 128.7, 128.7, 127.7, 126.6, 122.0, 21.3. Copyright of Synlett is the property of Georg Thieme Verlag Stuttgart and its content may not be copied or emailed to multiple sites or posted to a listserv without the copyright holder's express written permission. However, users may print, download, or email articles for individual use.