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(1*H*-BENZO[*d*][1,2,3]TRIAZOL-1-YL)METHANOL: AN EFFICIENT BIDENTATE LIGAND FOR COPPER CATALYZED S-ARYLATION OF THIOLS

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An operationally simple, palladium-free synthetic protocol for thio-arylation using 0.5 mol % CuI and 1 mol % (1*H*-benzo[*d*][1,2,3]triazol-1-yl)methanol as ligand is described. The ligand was found to be cheap, thermally stable, easy to synthesize, show simplicity in use and wide use in coupling reactions. Appropriately, the donor ability of the N=N bond of the benzotriazole ring and lone pair of electrons on the hydroxy group increases the bidentate ability of the ligand. Using this protocol, we have shown that a variety of aryl sulfides that can be synthesized in excellent yields from readily available aryl halide and thiols.

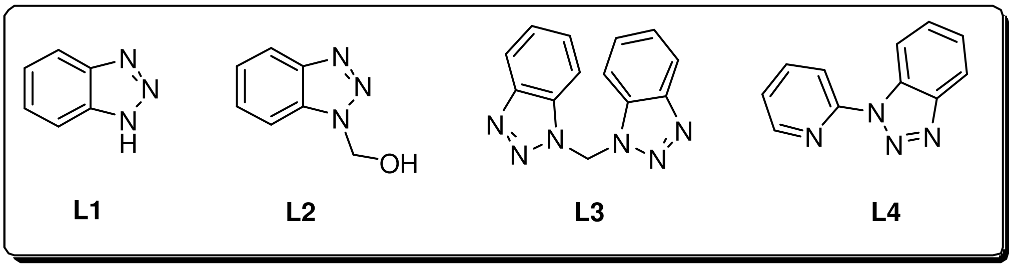
In the last decades, transition-metal catalyzed organosulfur chemistry brought an important progress in the field of biological, pharmaceutical, and materials interest.[1] Aryl sulphides are potentially demonstrated for diverse clinical application such as for the treatment of Alzheimer's, Parkinson's[2], cancer[3], and human immunodeficiency virus[4] diseases. However, transition-metal-mediated C(aryl)-S bond formation is a much less studied transformation than the corresponding C-N and C-O bond formations. The synthetic reaction involving sulfur-containing compounds possess special requirements because the sulfur functionality is highly reactive and may irreversibly deactivate the catalyst because of its strong coordinative properties[5]. So in recent years, many research groups have made great effort to overcome this problem and several excellent catalytic systems were used such as Pd[6], Cu[7], Ni[8], Fe[9], and other metals as catalysts have been found for C-S bond formation by couplings of aryl halides with thiols or disulfides[10].

In 1980, Migita and co-workers first reported the coupling between aryl halides and thiols using $Pd(PPh_3)_4$ as catalyst and NaO*t*-Bu as the base in polar solvents at 90°C[11]. Recently, few reports have came for carbon-sulfur bond formation based on nickel[12], cobalt[13], and palladium[14] since Migita's report. The reactivity behaviour of most of palladium catalysts are based on bidentate phosphines or diverse organophosphane derivatives[15]. Nevertheless, these system have still some limitations because of difficulty to prepare and environmentally unfriendly PR_3 ligands.

Consequently, there still is investigation in further development of the classical Ullmann's coupling reaction[1] applying cheap metals (e.g., copper) for the preparation of the diaryl thioether functionality. The major drawbacks of these kind of transformation are more catalyst loading, their short lifetime (and hence low turnover numbers), harsh reaction conditions, and often less scope. Therefore, different ideas have been applied in order to develop a general and more effective system for the preparation of diaryl thioethers. In this regard, attractive copper-catalyzed approach have recently been reported by our group[16], Palomo[17], Buchwald[18], Venkataraman[19], Domínquez[20] and others[21] using copper halide salts as the metal source together with a suitable ligand.

The stereoelectronic effects and the bite angle[22] of the *N,N* bidentate ligands are significant factors for the coupling reactions. Designed benzotriazole-based ligands are easy to prepare and are thermally and air stable. Appropriately, the donor ability of the N=N bond of the benzotriazole ring and lone pair of electrons on the OH group raise the bidentate ability of the ligand.

Katritzky's group have extensively explored benzotriazole as a synthetic stem due to its amazing



Ligands **L1-L4**, designed for various copper-catalysed coupling reaction

SCHEME-1

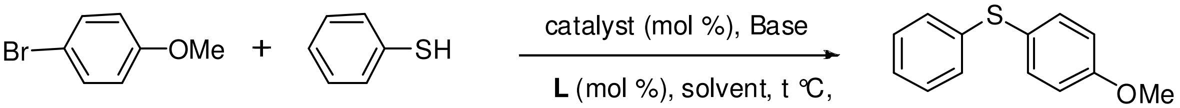
properties such as electron-donor as well as electron-acceptor properties with respect to the group attached to it[23]. In view of the above facts, and our recent success on the coupling reactions using benzotriazoles as a ligand[24,25] we were motivated for the design of a more efficient and practical ligand for the copper-catalyzed coupling reactions (Scheme 1).

Promoted by our current interest in carbon-carbon[26] and carbon-heteroatom coupling reactions, we decided to investigate the copper-catalyzed carbon-sulfur bond formation via the commercially available copper(I) halide salts. Herein, we report (1*H*-benzo[*d*][1,2,3] triazol-1-yl)methanol (**L2**) as a robust, palladium-free, phosphine-free, inexpensive and air stable bidentate ligand for the copper-catalyzed C-S coupling reaction. CuI was the chosen halide salt because of its stability to air. Catalytic tests performed with CuCl and CuBr, freshly prepared before use, gave the same results as obtained with commercially available CuI salt. Cu(II) salts tested ($CuBr_2$, $CuSO_4 \cdot 5H_2O$, $CuCl_2$) were found to be less efficient as catalysts (yields 25–35%) than the Cu(I) salts.

In order to find an optimal reaction condition, we selected electron-rich 1-bromo-4-methoxybenzene **2**a with benzenethiol **1**a as model substrates (Table 1). The reaction was performed with 5, 4, 3, 2, 1, 0.8 , 0.5 and 0.25 mol % of CuI and the corresponding equivalent amount (10, 8, 4, 2, 1, 0.8 and 0.5 mol %) of Ligands (**L1**, **L2**, **L3** and **L4**). We sought that all combination of CuI and ligands gave the desired product in good yields. The best result of coupling product **3**a was obtained using 0.5 mol % of CuI, 1 mol % of **L2** ligand, 1.4 equiv of base (KO*t*-Bu) in 2.0 mL of DMSO at 100° (Table 1, entry 10).

Table-1

Optimization of Reaction Conditions[a]



1a **2a** **3a**

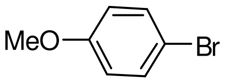
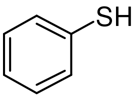
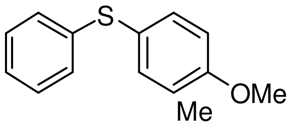
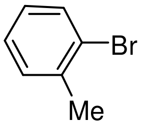
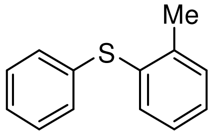
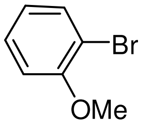
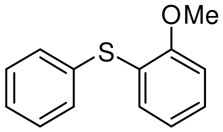
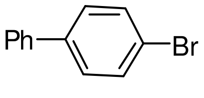
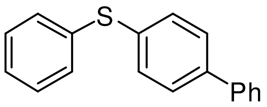
Entry	Catalyst	Base	Conditions			Ligand	Yield
	(mol %)		solvent	*t*℃	time (h)	(mol %)	(%)[b]
1	-	KO*t*-Bu	DMF	120	24	-	nd[c]
2	CuI (5)	KO*t*-Bu	DMF	120	18	L1(10)	88
3	CuI (5)	KO*t*-Bu	THF	100	18	L1 (8)	90
4	CuI (5)	KO*t*-Bu	dioxan	100	10	L2 (8)	93
5	CuI (5)	KO*t*-Bu	DMSO	100	10	L2 (8)	94

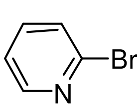
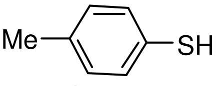
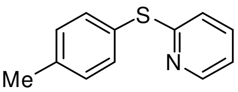
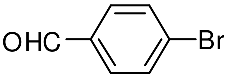
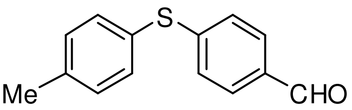
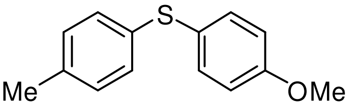
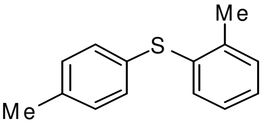
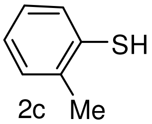
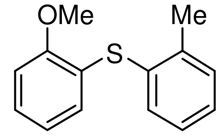
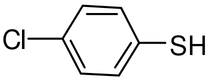
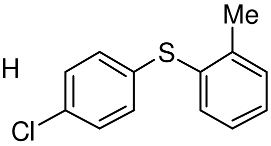
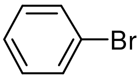
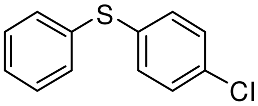
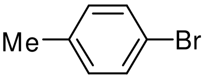
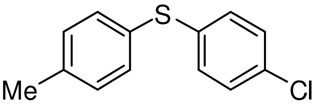
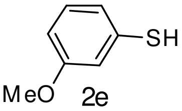
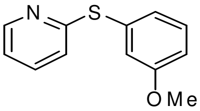
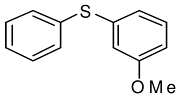
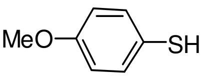
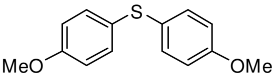
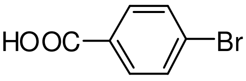
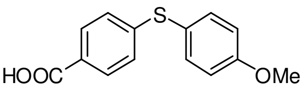
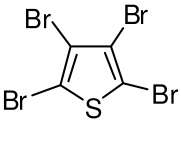
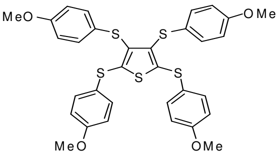
6	CuI (4)	KO*t*-Bu	DMSO	100	10	L3 (8)	91
7.	CuI (4)	KO*t*-Bu	DMSO	100	10	L4 (8)	93
7	CuI (5)	KO*t*-Bu	DMSO	100	8	L2(8)	94
8	CuI (2)	KO*t*-Bu	DMSO	100	8	L2 (4)	95
9	CuI (1)	KO*t*-Bu	DMSO	100	6	L2 (2)	96
10	**CuI (0.5)**	**KO*t*-Bu**	**DMSO**	100	**6**	**L2 (1)**	**97**
11	CuI (0.25)	KO*t*-Bu	DMSO	100	4	L2 (0.5)	90
12	CuI (0.5)	CS$_2$CO$_3$	DMSO	100	6	L2 (0.5)	80
13	CuI (0.8)	KO*t*-Bu	DMSO	100	4	L2 (0.8)	96

[a]The reactions were performed using 1.0 mmol of benzenethiol **1a**, 1.0 mmol of 1-bromo-4-methoxybenzene **2a**, 1.4 equiv. of base in 2.0 mL of solvent. [b]Isolated yields. [c]not determined

Using optimized conditions, variety of aryl bromides and arylthiols were evaluated and results are summarized in Table 2. Coupling of aryl bromides **1**a-d, **1**g-h with benzenethiol **2**a-f provided the corresponding products **3**a-d in 77-85% yields (Table 2, entries 1-4, 7-12, 14-15). Reaction of 2-bromopyridine **1**e with thiol **2**b and **2**e gave the S-arylated products **3**e and **3**m in 75 and 71% yields respectively at 80 °C (Table 2, entries 5 and 13). The coupling of bromoarenes with thiols was tolerant towards functional groups. Reaction of aryl bromides **1**f and **1**i bearing aldehyde and carboxylic groups that are incompatible with bases, gave the coupling products **3**f and **3**p in good yields using Cs$_2$CO$_3$ as base (Table 2, entries 6 and 16). Reaction of tetrabromo-thiophene **1**j with thiol **2**f provided the tetra-S-arylated product **3**q in 69% yield (Table 2, entry 17).

Table 2
Copper catalyzed coupling of aryl bromides with arylthiols using **L2** as ligand[a]

Entry	ArX		Thiol	Product		Yield (%)[b]
1		1a	 2a		3a	81
2		1b	2a		3b	83
3		1c	2a		3c	85
4		1d	2a		3d	77

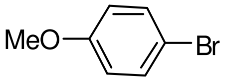
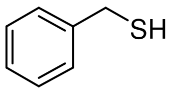
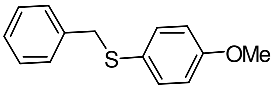
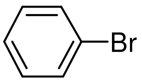
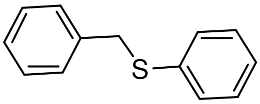
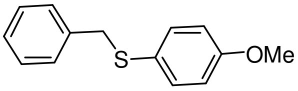
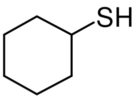
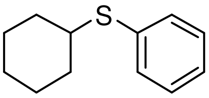
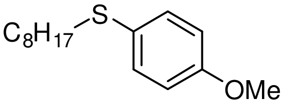
5		1e	 2b		3e	75^c
6		1f	2b		3f	70^d
7		1a	2b		3g	75
8		1b	2b		3h	79
9		1c	 2c		3i	78
10		1b	 2d		3j	82
11		1g	2d		3k	77
12		1h	2d		3l	76
13		1e	 2e		3m	71^c
14		1g	2e		3n	67
15		1a	 2f		3o	70
16		1i	2f		3p	68
17		1j	2f		3q	69^e

[a]The reactions were performed using aryl halide **1 (**1.0 mmol), benzenethiol **2** (1.2 equiv.), 1.4 equiv. of KO*t*-Bu, CuI (0.5 mol %) and **L2** (1.0 mol %) in 2.0 mL of DMSO solvent at 100 °C for 4–6 h. [b]Isolated yields. [c]At 80 °C. [d]Cs_2CO_3 was used as base. [e]Using thiol **2f** (4.0 equiv.), KO*t*-Bu (5.0 equiv.), CuI (1 mol %) and **L2** (2 mol %) in DMSO (4.0 mL) at 100°.

We further extended the scope of the developed protocol with aliphatic thiols. Alkylthiols were also found to be more effective nucleophiles under optimized reaction condition (Table 3). Coupling of aryl bromides **1**c, **1**g and **1**h with alkylthiol **2**g–i provided the coupling products **4**a–e in 77–86% yields (Table 3, entries 1-5).

Table-3

Copper catalyzed coupling of aryl bromides with alkylthiols using **L2** as ligand[a]

Entry	ArX		Thiol	Product		Yield (%)[b]
1		1c			4a	81
2		1g	2g		4b	83
3		1h	C_8H_{17}–SH 2h		4c	85
4		1g	 2i		4d	77
5		1c	2h		4e	86

[a]The reactions were performed using alkyl halide **1** (1.0 mmol), benzenethiol **2** (1.0 mmol), 1.4 mmol of KO*t*-Bu, CuI (0.5 mol %) and **L2** (1.0 mol %) in 2.0 mL of DMSO solvent at 80 °C for 4–6 h. [b]Isolated yields.

Probable Mechanism

In the light of these above preliminary results, a catalytic cycle for this transformation was proposed as shown in Scheme 2. Initially chelation of Cu(I) with **L2** ligand produced species **P,** which gives intermediate **Q** via oxidative addition of aryl halide. In the presencre of base, aryl and alkyl thiols react with intermediate **Q** rapidly to afford the possible intermediate **R.** After reductive elimination intermediate **R** provide the desired product **3** and regenerate the active CuI(I) species (Scheme-2).

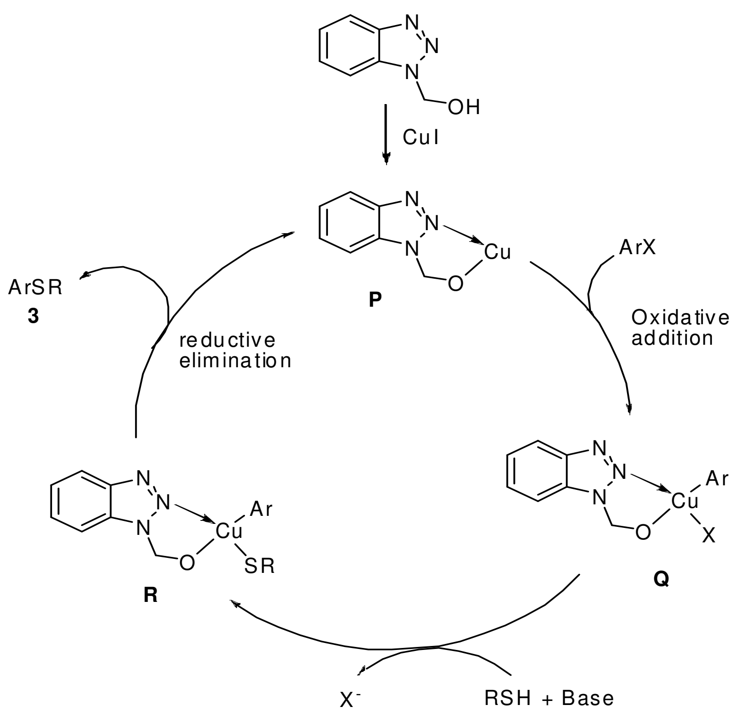
In summary, we have developed Cu(I)-catalyzed protocol which allowed a facile access to an impressive variety of C-S bond formation using air, moisture and thermally stable ligand **L2** from readily available starting materials in good to excellent yields under mild reaction conditions. The designed approach for the S-arylation is very general, palladium-free and avoids the use of PR_3 ligands.

Experimental

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for protons are reported in ppm from tetramethylsilane with the residual $CHCl_3$ resonance as internal reference. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. TLC analysis was performed on commercially prepared 60 F_{254} silica gel plates and visualized by either UV irradiation or by staining with I_2. Anhydrous forms of all reagents such as diethyl ether, hexanes, ethyl acetate, EDC, Et_3N, aryl halides, thiols and copper salts were used directly as obtained commercially unless otherwise noted.

Synthesis of Compound 3 and 4

To a solution of 1.0 mmol of aryl halide **1** in 2.0 mL of DMSO, was added 1.2 equiv. benzenethiol **2**, 1.4 equiv. of KO *t*-Bu followed by the addition of CuI



SCHEME-2

(0.5 mol %) and **L2** (1.0 mol %). The reaction mixture was allowed to stir at 80° to 100°C for 4–6 h. The disappearance of the starting material was determined by TLC. The reaction mixture was then washed with brine solution and was extracted with ethyl acetate (2 x 10 mL). The combined organic fractions were dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product. The crude product was purified by column chromatography on neutral alumina/silica gel using hexane/ethyl acetate as the eluent.

The structure and purity of the known final product **3**a–p^{23g}, **4**a–e^{23g} were confirmed by comparison of their physical and spectral data (^{1}H NMR and ^{13}C NMR) with those reported in literature.

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