



An efficient intermolecular C(aryl)–S bond forming reaction catalyzed by BINAM–copper(II) complex

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ABSTRACT

A wide range of diaryl thioethers and aryl alkyl thioethers are synthesized from the corresponding aryl iodides and aromatic/aliphatic thiols through Ullmann type intermolecular coupling reactions in the presence of a catalytic amount of easily available BINAM–Cu(OTf)₂ complex. Less reactive aryl bromides have also been shown to react with thiols under identical reaction conditions to give good yields of the thioethers without increasing the reaction temperature and time.

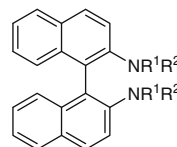
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C(aryl)–S bond containing molecules constitute a very important class of organic compounds playing a significant role in a number of chemical, material and pharmaceutical industries.¹ Traditional reaction conditions for the formation of this C–S bond require drastic conditions such as heating the reaction mixture at 200 °C in a polar solvent such as HMPA. Reduction of aryl sulfones or aryl sulfoxides is the alternative method for the synthesis of sulfides and it requires strong reducing agents such as DIBAL–H or LiAlH₄.² Later on, palladium-catalyzed C(aryl)–sulfur bond formation from the corresponding aryl halides and thiols became the method of choice.^{3,4} However, the high cost of palladium salts, high oxophilicity associated with phosphine ligands and tedious multi-step processes involved in the synthesis of these ligands have rendered Pd unpopular, particularly for large scale reactions.

The use of copper salt is an alternative for expensive palladium for the aryl–sulfur bond formation reaction from corresponding aryl halides and thiols. However, traditional copper-mediated reactions suffer from many drawbacks such as high reaction temperature, use of super stoichiometric copper salts, sensitivity to functional groups on the aryl halide and irreproducibility.⁵ In fact, only in the last few years considerable efforts have been taken to improve the efficiency of this reaction. They have now started to bear fruit with the use of copper salts with several ligands such as phosphazene,⁶ ethylene glycol,⁷ neocuproine,⁸ *N*-methyl glycine,⁹ oxime-phosphine oxide ligand,¹⁰ tripod ligand,¹¹ benzotriazole,¹² Cu nanoparticles,¹³ 1,2-diaminocyclohexane,¹⁴

β -ketoester¹⁵ and *L*-proline.¹⁶ It is thought that these ligands increase the efficiency of the Ullmann reaction by increasing the solubility of the copper salts by preventing their aggregation.

However, this advance in the field of Ullmann coupling is not sufficient as most of the reactions still require longer reaction times (more than 24 h), high reaction temperature (more than 110 °C) and in some cases, high catalytic loading. In particular, the coupling of aryl bromides with thiols does not provide the corresponding sulfides or provides only poor yields.^{9,13a,14} The catalyst loading or temperature has to be increased to improve the yields.^{9,14} Therefore a mild, economic and efficient catalytic system is still desirable for this C(aryl)–sulfur bond formation.



L1: R¹ = H; R² = Me

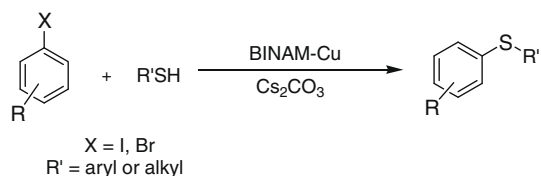
L2: R¹ = R² = Me

L3: R¹ = R² = H

L4: R¹ = H; R² = Bn

As part of our ongoing research in copper catalyzed oxidation chemistry,¹⁷ very recently, we reported a BINAM (1,1'-binaphthyl-2,2'-diamine) **L3**–Cu complex as an efficient catalyst for the synthesis of diaryl ethers and aryl alkyl ethers through Ullmann coupling.¹⁸ Thus, it was a natural extension for us to investigate the BINAM-copper catalyzed Ullmann type of coupling of thiols with aryl halides for the synthesis of important C(aryl)–S bond containing compounds (Scheme 1).

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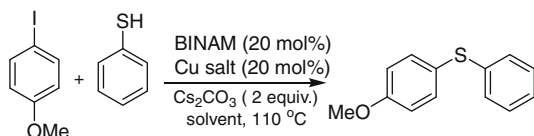


Scheme 1.

In preliminary studies, we used 20 mol % *N,N'*-dimethyl BINAM **L1** as a ligand with 20 mol % of $\text{Cu}(\text{OTf})_2$ for the coupling of *p*-methoxy iodobenzene with benzenethiol in DMF at 110 °C. *p*-Methoxy iodobenzene was fully consumed in 7 h and the reaction provided 85% isolated yield of the corresponding diaryl thioether. When ligand **L1** was replaced with *N,N'*-tetramethyl BINAM **L2**, the reaction provided 83% yield of the diaryl thioether. Surprisingly, on replacing ligands **L1** or **L2** by BINAM **L3**, the isolated yield for diaryl thioether increased to 96% in just 6 h. But replacing BINAM **L3** by *N,N'*-dibenzyl BINAM **L4**, the yield reduced to 83%. Next, the reaction was carried out with different ratios of BINAM and $\text{Cu}(\text{OTf})_2$ and it was found that 20 mol % of a ligand-copper combination was the most effective catalytic system to obtain quantitative conversion. The reaction provided only 30% thioether when only $\text{Cu}(\text{OTf})_2$ was used as a catalyst without BINAM. Importantly, not even a trace amount of thioether formed when the reaction was carried out without BINAM- $\text{Cu}(\text{OTf})_2$.

The reaction was screened with several copper salts, solvents and bases to increase the efficiency of the coupling reactions and the results are summarized in Table 1. Although several copper salts catalyzed the reaction, $\text{Cu}(\text{OTf})_2$ turned out to be the best copper salt of choice in view of reaction time and yield (Table 1, entry 1). Similarly, DMF was the best solvent among those examined. Cs_2CO_3 as base gave the best yields of the product in comparison with bases such as Na_2CO_3 and K_2CO_3 .

Table 1
Effect of Cu salts, solvents and bases



Entry	Cu salt	Solvent	Time	Yield ^a (%)
1	$\text{Cu}(\text{OTf})_2$	DMF	06 h	96
2	CuI	DMF	12 h	83
3	CuBr	DMF	21 h	87
4	CuCl	DMF	28 h	76
5	CuCl_2	DMF	35 h	67
6	$\text{Cu}(\text{OAc})_2$	DMF	38 h	80
7	CuSO_4	DMF	48 h	56
8	$\text{Cu}(\text{OTf})_2$	Toluene	48 h	52
9	$\text{Cu}(\text{OTf})_2$	DMSO	48 h	58
10	$\text{Cu}(\text{OTf})_2$	Dioxane	48 h	44
11	$\text{Cu}(\text{OTf})_2$	MeCN	11 h	90 ^b
12	$\text{Cu}(\text{OTf})_2$	THF	24 h	90 ^b
13	$\text{Cu}(\text{OTf})_2$	Xylene	24 h	53
14	$\text{Cu}(\text{OTf})_2$	DMF	15 h	80 ^c
15	$\text{Cu}(\text{OTf})_2$	DMF	24 h	54 ^d

^a Isolated yield.

^b Reactions were carried out in pressure tube.

^c K_2CO_3 was used as base.

^d Na_2CO_3 was used as base.

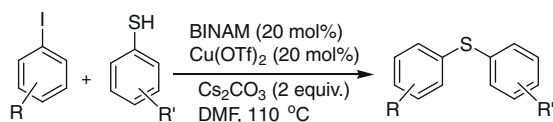
Using the above mentioned optimized conditions, we initiated our investigation into the scope of the BINAM- $\text{Cu}(\text{OTf})_2$ catalyzed Ullmann type coupling of aryl iodides with thiols and the results are summarized in Table 2. Various aryl iodides reacted with aromatic and aliphatic thiols to give the corresponding sulfides through a C(aryl)-S bond formation reaction. In the aryl iodide component, the presence of both electron-releasing groups such as methoxy and methyl groups or electron-withdrawing groups such as the nitro group were tolerated to give the corresponding thioethers in very high yields. Impressively, irrespective of its substitution in iodobenzene and whether it is in a *para* or *meta* position, the iodobenzene gave an excellent yield for the C(aryl)-S bond forming reaction. Similarly, in the case of thiols, both the aromatic and aliphatic thiols react with iodobenzene to give corresponding thioethers in excellent yields. In the case of aryl thiols, irrespective of whether it has *ortho* or *para* substitution, it gave an excellent yield for the aryl-sulfur bond forming reaction. An aromatic heteroatom containing thiols also gave excellent yields for the Ullmann coupling reaction with iodobenzene (entries 5 and 6).

We were pleased to note that under our optimized reaction conditions, aryl bromides also reacted with thiols to provide the corresponding thioethers. The reaction of simple bromobenzene with simple thiophenol provided 66% isolated yield for the corresponding thioether in 20 h (Table 3, entry 1). Having an electron releasing group either on bromobenzene or thiophenol or on both the reactants did not affect the course of the reactions (entries 2, 3 and 7). A heteroatom containing thiol and aliphatic thiol also reacted with aryl bromide to give corresponding thioether (entries 4 and 5).

However, the presence of electron-withdrawing groups such as nitro, cyano, or keto groups drastically increased the yield as well as the reaction rate (entries 8–11). Similarly, less reactive aryl tosylates also provided corresponding thioethers through a C(aryl)-sulfur bond forming reaction with thiols in the presence of BINAM- $\text{Cu}(\text{OTf})_2$ under optimized reaction conditions (entries 12–14). To our surprise, the coupling of *p*-acetyl tosylate with *p*-methyl thiophenol did not provide any corresponding thioether even after 24 h (entry 15). Interestingly, less reactive aryl chlorides also reacted with aromatic thiols under optimized reaction conditions to produce corresponding thioethers with excellent yields (Table 3, entries 18–20). When the chlorobenzene has nitro substitution in the *para*-position, it gave an almost quantitative yield for the coupling reaction by reacting with aromatic thiols. When the nitro group is replaced by other electron-withdrawing groups such as aldehyde, the yield was reduced by 10% and took a longer reaction time (entries 19, 20 vs 18). Replacing aldehyde or the nitro group of aryl chloride by a relatively weak electron-withdrawing group such as ester and amide failed to provide the thioether products (entries 16 and 17). Similarly, simple chlorobenzene or chlorobenzene with electron-releasing substituents failed to undergo the Ullmann coupling reaction with thiols. Since strongly activated aryl halide (aryl halides with very strong electron-withdrawing groups) can provide thioethers through the nucleophilic addition elimination mechanism, we carried out all the thioether formation reactions without our BINAM- $\text{Cu}(\text{OTf})_2$ catalyst under the same reaction conditions and strongly activated aryl halides such as *p*-nitro iodobenzene, *p*-nitro bromobenzene, *p*-cyano bromobenzene, *p*-chlorobenzaldehyde, and *p*-nitro chlorobenzene (Table 2, entry 14; Table 3, entries 8–14, 18–20) provided thioether product.

These results clearly show that the coupling reaction is favoured in C-S bond formation in the case of simple aryl halide and the electron-releasing group containing aryl halides. In the case of strongly activated aryl halides and tosylates (having nitro and cyano groups), the nucleophilic addition elimination mechanism dominates, this is evident since it performs reactions with-

Table 2
Coupling of aryl iodides with thiols¹⁹

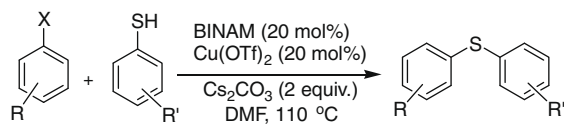


Entry	Aryl iodide	Product	Time (h)	Yield ^a (%)
1			6	96
2			6	97
3			5	97
4			8	96
5			8	94
6			12	88
7			4	97
8			10	88
9			6	96
10			6	97
11			7	95
12			6	94
13			8	95
14			4	87 ^b

^a Isolated yield. All the thioethers gave satisfactory spectral data. See Supplementary data for details.

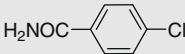
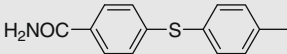
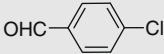
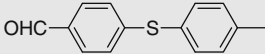
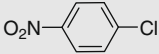
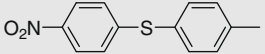
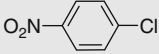
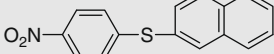
^b The reaction took place without BINAM-Cu(OTf)₂.

Table 3
Coupling of aryl bromides/aryl tosylates/aryl chlorides with thiols



Entry	Aryl halide/tosylate	Product	Time (h)	Yield ^a (%)
1			20	66
2			24	67
3			21	61
4			24	53
5			17	64
6			20	66
7			17	65
8			8	86 ^b
9			8	90 ^b
10			8	84 ^b
11			8	84 ^b
12			8	87 ^b
13			8	86 ^b
14			8	81 ^b
15			24	00
16			24	00

Table 3 (continued)

Entry	Aryl halide/tosylate	Product	Time (h)	Yield ^a (%)
17			24	00
18			18	87 ^b
19			5	98 ^b
20			5	97 ^b

^a Isolated yield. All the thioethers gave satisfactory spectral data. See Supplementary data for details.

^b The reaction took place without BINAM–Cu(OTf)₂.

out a catalyst. In the case of weakly activated aryl chlorides, neither the nucleophilic addition elimination mechanism nor the coupling reaction catalyzed by BINAM–Cu(OTf)₂ provides the product (Table 3, entries 16–17). This result shows that highly activated aryl halides (aryl halides with very strong electron-withdrawing groups such as nitro and aldehyde groups) give C(aryl)–S bond formation through the nucleophilic addition elimination mechanism) without a copper catalyst, whereas other aryl halides need a copper catalyst for C–S bond formation through the coupling reaction.

In summary, we have developed an efficient, experimentally simple and economically attractive copper catalyzed S-arylation of thiols with aryl iodides. Aryl bromides can also be used for S-arylation of thiols under the same reaction conditions without increasing the reaction temperature. Strongly activated aryl chlorides and tosylates provide corresponding thioethers by the nucleophilic addition elimination mechanism without a copper catalyst. Efforts to expand the utility of our new catalytic system to weakly activated chlorides/tosylate and other classes of nucleophiles and detailed mechanistic studies are in progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.022.

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- Typical representative experimental procedure: Cs₂CO₃ (325.8 mg, 1 mmol), Cu(OTf)₂ (36.16 mg, 0.1 mmol) and BINAM **L3** (28.4 mg, 0.1 mmol) were taken in a 10 mL reaction tube equipped with a septum. The reaction tube was evacuated and back-filled with nitrogen. *N,N*-Dimethylformamide (2.0 mL) was added to the reaction mixture at room temperature. To the resulting solution, *p*-methoxy iodobenzene (117 mg, 0.5 mmol) was added followed by benzenethiol (60.6 mg, 0.55 mmol), and the reaction mixture was heated for 6 h at 110 °C. After the complete disappearance of *p*-methoxy iodobenzene (the progress of the reaction was monitored by TLC), the reaction mixture was allowed to cool to room temperature. The crude residue was directly purified by column chromatography on silica gel using ethyl acetate/hexanes as eluents to give 96% of pure 4-methoxyphenyl phenyl sulfide⁸ (Table 2, entry 1) as colourless oil.