



An efficient tris-(2-aminoethyl)amine-CuI-catalyzed thioetherification of thiols with aryl halides

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ABSTRACT

A robust method has been developed to couple a wide variety of thiols and aryl halides. The C–S bond forming reaction makes use of catalytic copper(I) iodide and the ligand tris-(2-aminoethyl)amine. These conditions tolerate a wide degree of functionality on both aryl halide and thiol reactants and have resulted in numerous examples being synthesized. Commercial availability of the ready to use, inexpensive ligand, tris-(2-aminoethyl)amine and air-stable CuI make the method well suited to generate a diverse array of diaryl thioethers.

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Aryl sulfides are valuable subunits for organic synthesis and are an integral part of numerous drugs in therapeutic areas such as treatment of Alzheimer's and Parkinson's disease,¹ treatment of cancer,² and in many molecules that are of biological, pharmaceutical, and material interest.³ Traditionally, the Ullmann-type coupling is a straightforward method to form the requisite carbon–sulfur (C–S) bond via coupling of thiol-containing substrate to an aryl halide.^{3e,4} However, the harsh reaction conditions such as high temperatures, strong bases, stoichiometric amounts of copper salts, and long reaction times effect the transformations and act as severe limitations in the reaction, especially on a large scale. The use of copper or its salts in stoichiometric ratio adds hazardous waste to the environment making the process environmentally unfriendly.

In contrast to the carefully investigated arylation reactions of amine, amide, and alcohol, metal-catalyzed thioether formation has received only little attention. Knowing that the transition-metal-catalyzed S-arylation has been less emphasized, recently much attention has been laid on the C–S bond formation. Migita et al.⁵ first reported the coupling of aryl halides with thiols using Pd(PPh₃)₄ as a catalyst under mild conditions. Recent improvements using palladium-catalyzed thioetherification include general protocols by Zheng et al. using aryl triflates⁶ and a coupling using DPEPhos as ligand by Schopfer and Schlapbach.⁷ Hartwig and co-workers reported thioetherification using CyPF-*t*-Bu as the ligand.⁸ Even though significant improvements have been achieved in Pd-catalyzed S-arylation reactions, it remains hard to

apply these reactions to large and industrial scale syntheses due to the high cost of palladium and its corresponding bulky phosphine ligand. Moreover, these protocols pose a difficulty in removing palladium residues from the polar reaction products and add hazardous waste to the environment during the synthesis of bulky phosphine ligands.

The C–S coupling protocol was made attractive from an economic standpoint with the use of copper as an alternative to palladium. An interesting finding that the S-arylation can be facilitated by certain organic ligands has led to a wide survey of different ligands that could be coupled with copper. Up to now, the ligands that have been found to promote the Cu-catalyzed thioetherification reaction include benzotriazole,⁹ neocuproine,¹⁰ β-keto ester,¹¹ *trans*-cyclohexan-1,2-diol,¹² BINAM–Cu(OTf)₂,¹³ and ethylene glycol.¹⁴ Though the reports promise the development of novel methods, viable, inexpensive, and commercially available ready to use ligands for thioetherification are still in demand. There is still a pressing need for the development of a novel Cu–ligand catalyst system for thioether formation.

We have recently used CuI-tris-(2-aminoethyl)amine catalyst system for diaryl ether formation.¹⁵ Inspired by the results, we intended to extend our campaign of carbon–heteroatom bond formation. Here, we would like to report the CuI-catalyzed S-arylation of aryl halides with thiols using tris-(2-aminoethyl)amine as an effective ligand. The protocol offers a highly general, convenient, and inexpensive catalyst system for S-arylation of thiols with both aryl iodides and aryl bromides. This protocol also shows high levels of functional group compatibility on both aryl halides and thiols.

During the course of our study, we have screened many different combinations of ligands, bases, solvents, and reaction temper-

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atures in order to maximize the coupling yield. A comparative study of the reaction conditions and results for the CuI-catalyzed thioetherification using the methods described above and that reported in the present Letter clearly demonstrate the generality and efficacy of the present methodology.

As indicated in Table 1, our experiments were first conducted by coupling thiophenol with iodobenzene catalyzed by 5 mol % of copper(I) iodide and 5 mol % of L [tris-(2-aminoethyl)amine]. The reaction proceeded to produce the desired coupling product in 79% yield (Table 1, entry 1). Increasing the amounts of CuI:L to 10 mol % gave higher yields (88%, Table 1, entry 2). Further increasing the amounts of CuI:L to 15 mol % and 20 mol % (Table 1, entries 3 and 4) showed only a marginal rise in the yields of the coupled product (compare entries 2–4). This indicates that 10 mol % is the necessary and sufficient proportion of CuI and L for this thioetherification protocol. Our attempts to test the efficacy of the monodentate, 2-methylpropan-2-amine as a ligand in this protocol proved futile, as it furnished no product (Table 1, entry 5). Moreover, the bidentate, *N*-(2-aminoethyl)ethan-1,2-diamine yielded the coupled product in only 43% isolated yield (Table 1, entry 6). Without the addition of the ligands, no coupling reaction occurred (Table 1, entry 7), which clearly showed that the presence of tris-(2-aminoethyl)amine was necessary for this reaction. The above-mentioned study clearly determines the efficacy of the tripod ligand, tris-(2-aminoethyl)amine.

Various solvents were screened using CuI-tris-(2-aminoethyl)amine as a catalyst system (Table 1), and the best results were obtained with 1,4-dioxane as a solvent. Reactions were carried out at 110 °C for dioxane and *N,N'*-dimethylformamide as sol-

vents (Table 1, entries 2 and 10). The use of less polar solvent like toluene at the same temperature yielded 62% of the coupled product (Table 1, entry 8). The use of polar and high boiling solvents like DMF, NMP, and DMSO furnished 73%, 75%, and 74% product, respectively (Table 1, entries 10–12). 1,2-Dimethoxyethane (DME) having similar polarity as that of dioxane yielded only 68% of the product (Table 1, entry 13). The use of isopropanol and acetonitrile as solvents produced only 53% and 72% product, respectively (Table 1, entries 9 and 14). Thus, dioxane was confirmed to be the most effective solvent for this reaction.

Several bases were screened for the coupling reaction using 10 mol % of CuI and 10 mol % of tris-(2-aminoethyl)amine as ligands. When K₂CO₃ and KOH were used as bases, the coupling reaction produced only 42% and 44% of the product, respectively (Table 1, entries 15 and 19). Inorganic bases such as K₃PO₄, which are widely used in Cu-catalyzed protocols for the C–N, C–O, and C–S bonds,¹⁶ afforded the desired thioether only in moderate yield (68%, Table 1, entry 16). The use of *t*-BuOK as a base furnished only 57% of the product (Table 1, entry 17). Similar to the yields of *t*-BuOK, organic bases like triethylamine produced only 53% (Table 1, entry 18) of the coupled product. On the basis of the study of bases, it is quite clear that the Cs₂CO₃ that yielded the product in 88% yield (Table 1, entry 2) is the base of choice for this thioetherification protocol.

On the basis of the aforementioned studies, we concluded that using tris-(2-aminoethyl)amine (10 mol %) as the ligand, dioxane as the solvent, Cs₂CO₃ (2 equiv) as the base and carrying out the reaction at 110 °C are optimized conditions (Scheme 1). To investigate the scope of the reaction, a variety of aryl iodides were used (Table 2). For aryl iodides, it is found that a variety of substituents at either *ortho*, *meta*, or *para* position can be tolerated in the S-arylation protocol. In particular, electron-deficient aryl iodide (Table 2, entries 6 and 7) works fairly well in the coupling, furnishing the product in 86%¹⁷ and 90% yield, respectively. An aryl iodide with *ortho*-substituent (Table 2, entries 2 and 5) is not a problem with the CuI-tris-(2-aminoethyl)amine catalyst system producing the coupled product in 83% and 84% yield, respectively. Hence, it is clear that the electron-rich aryl iodides are also compatible with these conditions, delivering S-arylation product in good yields. The electron-deficient aryl iodides were generally superior to the electron-rich ones as evidenced by the slightly better yields and shorter reaction time.

During our study to determine the scope of the catalytic system, the present protocol was applied also to a diverse array of thiophenols. The result showed that thiols containing electron-withdrawing group could provide lower yields than the ones containing electron-donating group. The thiol containing a methoxy group at *para*-position could produce thioether in 89% yield (Table 2, entry 9) and 3,5-dimethylthiol could furnish 87% of the S-arylated product (Table 2, entry 8). The electron-withdrawing chloro-substituent showed its presence by reducing the yield to 68% (Table 2, entry 10).

We next examined aryl bromides as the substrates for our catalytic system and were pleased to find that the coupling of thiophenol with bromobenzene took place, producing the desired thioether in 86% yield (Table 2, entry 11). In contrast to this, the

Table 1
Effect of CuI, ligand, base, and solvent on coupling of thiophenol with iodobenzene

Entry	CuI (mol %)	Base	Solvent (temp °C)	Yield ^a (%)
1	CuI (5)	Cs ₂ CO ₃	1,4-Dioxane (110)	79
2	CuI (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	88
3	CuI (15)	Cs ₂ CO ₃	1,4-Dioxane (110)	89
4	CuI (20)	Cs ₂ CO ₃	1,4-Dioxane (110)	89
5	CuI (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	No reaction ^b
6	CuI (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	43 ^c
7	CuI (10)	Cs ₂ CO ₃	1,4-Dioxane (110)	Trace ^d
8	CuI (10)	Cs ₂ CO ₃	Toluene (110)	62
9	CuI (10)	Cs ₂ CO ₃	Isopropanol (80)	53
10	CuI (10)	Cs ₂ CO ₃	DMF (110)	73
11	CuI (10)	Cs ₂ CO ₃	NMP (130)	75
12	CuI (10)	Cs ₂ CO ₃	DMSO (130)	74
13	CuI (10)	Cs ₂ CO ₃	DME (85)	68
14	CuI (10)	Cs ₂ CO ₃	Acetonitrile (82)	72
15	CuI (10)	K ₂ CO ₃	1,4-Dioxane (110)	42
16	CuI (10)	K ₃ PO ₄	1,4-Dioxane (110)	68
17	CuI (10)	<i>t</i> -BuOK	1,4-Dioxane (110)	57
18	CuI (10)	Triethylamine	1,4-Dioxane (110)	53
19	CuI (10)	KOH	1,4-Dioxane (110)	44

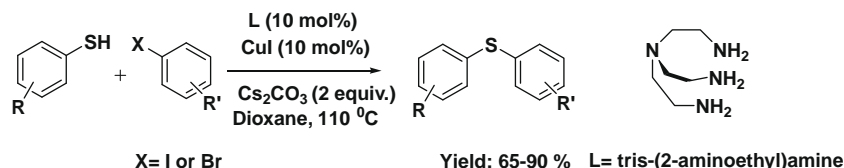
Reaction conditions: Thiol (1 mmol), alkyl halide (1 mmol), L (10 mol %), CuI (10 mol %), base (2 equiv), and solvent (3 ml).

^a Isolated yields.

^b 2-Methylpropan-2-amine used as a monodentate ligand.

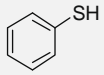

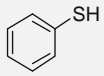

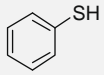

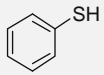
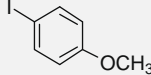
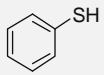

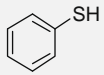
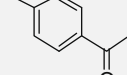
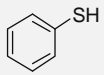
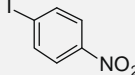
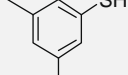

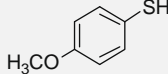

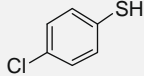

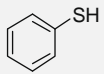

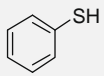
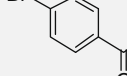
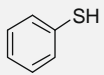
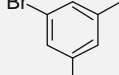
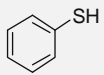
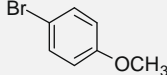
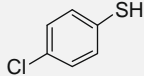

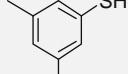

^c *N*-(2-Aminoethyl)ethan-1,2-diamine used as a bidentate ligand.

^d In the absence of a ligand.



Scheme 1. Coupling of thiol with aryl halide using CuI-tris-(2-aminoethyl)amine catalyst system.

Table 2
Coupling of thiol with aryl halide using CuI-tris-(2-aminoethyl)amine catalyst system

Entry	Thiol	Aryl halide	Time (h)	Yield ^a (%)
1			20	88
2			18	84
3			18	84
4			19	82
5			20	83
6			18	86
7			17	90
8			18	87
9			18	89
10			20	78
11			20	86
12			21	85
13			23	82
14			23	80
15			24	65
16			22	84

^a Isolated yields after column chromatography.

protocol by Chen and Chen was not shown to couple aryl bromides with thiols.¹⁸ All the other bromides, whether electron-rich (Table 2, entries 13 and 14) or electron-poor (Table 2, entry 12), worked well under these conditions. In these cases good conversions were observed, although slightly longer reaction time was required compared with that required for aryl iodides. Like aryl iodides, aryl bromides with an electron-withdrawing group (Table 2, entry 12) showed better reactivity compared with those bearing electron-donating groups (Table 2, entries 13 and 14). The products obtained by this method have been well characterized by physical and spectroscopic data.

In conclusion, we have developed an operationally simple, efficient, and general methodology for the copper-catalyzed thioetherification reaction of aryl halides with thiols using commercially available, inexpensive tripod ligand, tris-(2-aminoethyl)amine. These conditions tolerate a wide degree of functionality on both the partners as shown by the numerous examples synthesized and broaden the scope of C–S bond forming reactions. Efforts to expand the utility of the protocol to other types of carbon–heteroatom bond-forming reactions in combination with mechanistic studies are in progress.

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- Representative procedure:** Coupling of 4-iodoacetophenone and thiophenol (Table 2, entry 6): Into a 25 ml capacity one neck round-bottomed flask was charged dioxane (3 ml) followed by ligand **L** (0.1 mmol), CuI (0.1 mmol), 1-(4-iodophenyl)ethanone (1 mmol), thiophenol (1.02 mmol), and Cs₂CO₃ (2.04 mmol). The reaction mixture was stirred with a magnetic stir bar and heated to 110 °C in an oil bath for 18 h. The completion of the reaction was monitored by TLC. After the complete consumption of 1-(4-iodophenyl)ethanone, the reaction mixture was cooled to room temperature and water (20 ml) was added. The crude mixture was extracted with ethyl acetate and purified by column chromatography on silica gel to afford 4-phenylsulfanylacetophenone (0.087 g, 86%) as white solid. ¹H NMR (CDCl₃, 400 MHz, δ ppm): 7.80 (2H, d), 7.48–7.50 (2H, m), 7.38–7.40 (3H, m), 7.19 (2H, d), 2.53 (3H, s). ¹³C NMR (50 MHz, CDCl₃, δ ppm): 26.3, 127.4, 128.6, 128.8, 129.5, 132.0, 133.6, 134.4, 144.7, 197.0. The spectroscopic data are in full agreement with those described in the literature.^{10,11,18}
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