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A general and inexpensive protocol for the Cu-catalyzed C-S cross-coupling reaction between aryl halides and thiols

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ABSTRACT

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Keywords: Catalysis Copper C-S coupling DABCO Thioetherification A cost effective and easily available CuI/DABCO catalytic system has been developed for C-S cross-coupling reaction. This method is extremely useful for the thioetherification of aryl and heteroaryl halides providing excellent yields and good chemoselectivity

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Introduction

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Transition metal catalyzed C-S coupling reactions have gained considerable attention in recent years because of the prevalence of these moieties in many important compounds of biological, pharmaceutical or material interest.¹ The traditional methods for C-S bond formation require high temperature, polar solvents or strong reducing agents.² However the discovery of Pd-catalyzed C-S coupling by Migita and co-workers was a breakthrough in this area and it provided a novel pathway for the preparation of thioethers.³ Unfortunately the high cost of Pd salts, low turnover numbers and sensitivity to air limited its application on an industrial scale unless highly efficient or recyclable catalyst is used. These constraints prompted the search for other viable tools for this transformation with wide substrate scope and better functional group tolerance. In this regard, other transition metal catalyzed C-S coupling reactions have emerged in recent years.⁴⁻ ^{13.} As part of our ongoing research in transition metal catalyzed coupling reactions, we recently reported Zn and Fe-catalyzed C-S coupling reactions.^{8a,13} In continuation of our efforts to develop a more cheaper catalyst with better yield and functional group tolerance we focused on Cu catalysts. Cu has certain advantages such as low toxicity, low cost and is compatible with many readily available and cheap ligands. In addition, Cu has readily accessible coordination numbers 2, 3 and 4, which allows it to play a significant role in many catalytic reactions.^{1f} Herein, we report CuI/DABCO catalytic system as a general tool for the C-S cross-coupling reaction avoiding the use of expensive Pd-based catalytic system. The ligand DABCO is very cheap and readily available and when used in combination with air stable CuI, it provides an excellent catalytic system that can be used for the synthesis of electronically diverse alkyl, aryl and heterocyclic sulfides providing excellent yields in short reaction time. Furthermore the excellent chemoselectivity of this method enabled the synthesis of 4-(4-Nitrophenylsulfanyl)phenylamine, which is otherwise difficult to obtain from metal-catalyzed coupling reactions. 4-(4-Nitrophenylsulfanyl)phenylamine can be used as the precursor for the synthesis of Dapsone, a drug for the treatment of leprosy.14

Results and discussion

In order to explore the efficiency of various copper based catalysts for C-S cross-coupling reactions, the coupling of 4-iodoanisole with thiophenol was chosen as the model reaction. The results of the optimization studies are summarized in table 1.

Table 1

Optimization studies for Cu-catalyzed C-S cross-coupling reaction between 4-iodoanisole and thiophenol.^[a]

$MeO \xrightarrow{I + HS} \underbrace{Cul, Ligand}_{Base, Solvent, 12h} MeO \xrightarrow{S} \underbrace{Cul}_{Base, Solvent, 12h} MeO \xrightarrow{S} \underbrace{Cul}_{AeO}$					
L ₁ L ₂		L ₂	L ₃	L_4	
Entry	Ligand	Solvent	Base	Temperature	Yield
				(°C)	(%) ^[b]
1	L_1	DME	K_2CO_3	80	8
2	L_2	DME	K_2CO_3	80	32

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3	L_3	DME	K_2CO_3	80	12
4	L_4	DME	K_2CO_3	80	34
5	L_4	DME	K_2CO_3	120	98
6	L_4	DME	K_2CO_3	RT	-
7	L_4	CH ₃ CN	K_2CO_3	120	93
8	L_4	Water	K_2CO_3	120	31
9	L_4	Toluene	K_2CO_3	120	45
10	L_4	DMF	K_2CO_3	120	53
11	L_4	THF	K_2CO_3	120	93
12	L_4	DMSO	K_2CO_3	120	59
13	L_4	t-BuOH	K_2CO_3	120	65
14	L_4	DME	Na ₂ CO ₃	120	85
15	L_4	DME	K ₃ PO ₄	120	80
16	L_4	DME	NaO'Bu	120	81
17	L_4	DME	KO'Bu	120	96
18	L_4	DME	TEA	120	96
19	L_4	DME	-	120	69
20	_	DME	K ₂ CO ₃	120	Trace

[a]: Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), CuI (10 mol%), Ligand (20 mol%), Base (2 equiv.), 120 °C, 12 h, N_2 , [b]: isolated yield, [c]: 2.2 equiv. of DABCO was used.

The success of cross-coupling greatly depends upon the choice of ligand, and therefore we first examined the effect of some inexpensive N,N and N,O bidentate ligands for the C-S crosscoupling reaction by taking 4-iodoanisole and thiophenol as the model substrates, and air stable CuI as the metal source in the presence of K₂CO₃ and DME. Initially all experiments were performed using 10 mol% CuI and 20 mol% of ligand for 12 h under N₂ atmosphere at 80 °C. To our delight, the use of ligand L₄ (DABCO) resulted in 34% isolated yield of the C-S coupled product in 12 h (table 1, entry 4). Further increasing the temperature to 120 °C resulted in a sharp increase in the yield of the product to 98% (table 1, entry 5). As expected, lowering the reaction time or temperature showed a negative effect on the yield of the reaction (supporting information, table 1, entries 4 & 7).).Thus we selected DABCO, which is very cheap and easily available, as the suitable ligand for this coupling reaction. The use of DABCO as an efficient ligand for other metal-catalyzed coupling reactions has already been reported in literature.¹⁵ We further explored the effect of different bases, solvents and catalyst loading. The screening of different solvents revealed that DME is superior to other solvents (table 1, entries 7-13). Choosing DME as the solvent and DABCO as the ligand, we screened different inorganic and organic bases and found that K₂CO₃, KO^tBu and triethylamine are excellent bases for this coupling reaction (table 1, entries 14-18). A blank experiment revealed that only trace amount of the product could be formed in the absence of Cu-catalyst or ligand (supporting information, table 1, entries 21 & 22). We also tested the possibility of using DABCO as a ligand and a base, but in that case the yield of the product dropped to 69% (table 1; entry 19). Notably, when the reaction was carried out in aerobic atmosphere, the yield of the product was reduced due to the formation of significant amount of disulfide (supporting information, table 1; entry 23). Next, we investigated the effect of catalyst loading and found that 5 mol% CuI and 10 mol% DABCO is the most suitable combination to afford maximum yield (table 2, entry 1). To understand how the copper:ligand ratio affects the reaction, we performed the reaction by taking a 1:1 ratio of Cu salt:ligand and found that the

yield of the product was reduced to half (table 2, entry 4). Further studies revealed that a 1:2 ratio of copper:ligand is needed presumably to make a 4-coordinated Cu-ligand complex.

Table 2

Optimization of catalyst loading.^[a]

Entry	CuI	DABCO	Yield
	(mol%)	(mol%)	(%) ^[b]
1	5	10	98
2	10	20	98
3	20	40	92
4	5	5	57

[a]: Reaction conditions: 4-iodoanisole (0.6 mmol), thiophenol (0.5 mmol), K_2CO_3 (2 equiv.), DME (3 ml), 120 °C, 12 h, N_2 , [b]: isolated yield.

Thus the optimal condition for C-S cross-coupling reaction is 5 mol% CuI, 10 mol% DABCO and 2 equiv of K_2CO_3 in DME at 120 °C.

We then applied the optimized reaction conditions to a broad range of substrates. Both electron rich and electron deficient thiophenols effectively coupled with various aryl iodides giving excellent yields of the product (table 3, entries 1-15). Coupling of heterocyclic compounds which are prevalent in many biologically active compounds often seems to be difficult to synthesize with metal-catalyzed coupling reactions.¹⁶ But the present protocol is successfully applied to the coupling of heterocyclic aryl iodides as well giving excellent yields of the sulfides (table 3, entries 12 & 13). Furthermore, the reaction is not much sensitive to steric effects as evidenced by the reaction of sterically demanding 2-iodoanisole which also afforded 96% yield of the product (table 3, entry 7). More importantly, aryl bromides also worked well for this reaction (table 3, entries 2, 4, 8 & 14) and could be extended to aryl chlorides also (table 3, entry 5). Unfortunately when 4-bromotoluene was reacted with thiophenol and 4-methylthiophenol, the required products were detected in GC-MS, but we could not separate the required sulphide product from the disulfide by-product formed by homocoupling during the reaction. With aryl triflate and thiophenol, only a trace amount of the product was obtained. The product in entry 15 can be used as a precursor for the preparation of Dapsone, a drug used in the treatment of leprosy. Next, we extended this methodology to aliphatic thiols, which also afforded excellent yields of the product when reacted with aryl iodides having both electron donating or electron withdrawing groups (table 3, entries 16-21).

The present catalytic system holds several advantages over the Zn and Fe- based catalytic systems reported by us.^{8a,13} The CuI/ DABCO catalytic system has better yield, low cost and requires only less catalyst loading in comparison with the Zn and Fe catalytic systems. Moreover, sensitive functional groups like NH₂ also afforded good yields of the product with the CuI/ DABCO system.

Table 3

Substrate scope of the Cu-catalyzed C-S cross-coupling between aryl iodides and thiols.^[a]

Ar-X	+ R-SH	DABCO (10 mol%)	Ar S B	
R = aryl	, alkyl	K ₂ CO ₃ (2 equiv),DME	=	
Entry	ArX	RSH	Product	Yield (%) ^[b]
1	H ₃ CO	SH SH	H ₃ CO Sa	98
2	H ₃ CO	Br SH	H ₃ CO 3a	60 ^[c]
3	H3COC	JI JSH	H ₃ COC 3b	99
4	H3COC	Br SH	H ₃ COC 3b	78
5	H3COC	CI SH	H _a coc 3b	28
6		SH	GF3 3c	90
7		DMe	S OMe	96
8	B	Ne SH		49 ^[c]
9	NC	SH SH	NC 3e	97
10	H3COC	HS OMe	H ₃ COC 31 OMe	95
11	NC	HS OMe	NC 3g OCH3	90
12		SH	S N 3h	94
13		HS CH3	S N 3i CH3	88
14	NC	Br	H ₃ C S CN	58 ^[d]
15	O ₂ N	HS NH ₂	O ₂ N 3k NH ₂	96 ^[d]
16		SH	S 3I	97
17	CF3	SH SH	S CF _a 3m	99
18	H ₃ CO	ј ́	H ₃ CO S	89

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[a]: Reaction conditions: ArX (0.6 mmol), thiol (0.5 mmol), CuI (5 mol%), ligand (10 mol%), base (2 equiv), 120 $^{\circ}$ C, N₂, [b]: isolated yield, [c]: 1.6 equiv. of thoiophenol is used and reaction carried out for 24h. [d]: Reaction was carried out for 17 h.

Mechanistic Rationale

On the basis of the above observations we propose a possible reaction pathway for the copper (I) catalyzed C-S cross-coupling reaction of aryl halides with thiols (Scheme 2).

Scheme 2

Plausible reaction mechanism



Even though DABCO is a bidentate ligand, the two N atoms cannot coordinate with the same Cu atom since they are 180° apart from each other. Thus DABCO-Cu complex may exist as an oligomer or as a dimer, where two Cu atoms are linked through a DABCO molecule as a bridge.¹⁷ It is presumed that in the first step, CuI gets coordinated with the ligand DABCO and forms a dimeric Cu (I) complex I which is consistent with the Cu:ligand ratio in the reaction (table 2). This complex formation may increase the solubility of the Cu salt in organic solvents. In the next step, oxidative addition of aryl halide can occur and furnishes a Cu (III) complex II. The thiolate anion generated in the presence of base can then get exchanged with the halogen and forms the complex III which can then undergo reductive elimination to give the required product. The regenerated Cu(I)-catalyst can then enter into the next catalytic cycle. Further

efforts to probe the mechanism using EPR studies are still going on in our laboratory.

Conclusion

In summary, we have developed a versatile, simple and economical C-S cross-coupling reaction which can be applied for the coupling of aryl or heteroaryl iodides with alkyl and aryl thiols. The CuI/DABCO catalytic system is very cheap, readily available and shows excellent chemoselectivity. These features are highly useful when considering the scaling up of the reaction. Further efforts to elucidate the mechanism and expand the scope of the reaction are currently underway.

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