

A general and efficient CuI/BtH catalyzed coupling of aryl halides with thiols

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Abstract—We report an exceptionally mild, general and efficient copper catalyzed cross coupling reaction of aryl bromides and thiols using 0.5 mol % CuI and 1 mol % benzotriazole. Experimental simplicity, generality, functional group tolerance and low cost of the catalyst are advantages of the protocol.

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Aryl sulfides are of great significance to the pharmaceutical industry¹ and are a common functionality found in numerous drugs in therapeutic areas such as diabetes and anti-inflammatory, and Alzheimer's and Parkinson's diseases.² The traditional method for C–S coupling is a substitution reaction via an addition–elimination mechanism,^{3e,f} which often requires a high temperature and long reaction times or substrates with electron withdrawing groups. Transition metal-catalyzed and mediated C–S couplings usually require harsh reaction conditions.³ Migita and co-workers^{4a,b} first reported the coupling of iodo and bromo arenes with thiols using Pd(PPh₃)₄ as the catalyst under mild conditions, and many ligands have now been tested for this reaction.^{4,5} More recently, Hartwig and co-workers reported palladium catalyzed C–S coupling using CyPF-*t*-Bu as the ligand.⁴ⁱ Metal-catalyzed C–S bond formation from aryl triflates has also received attention being an alternative to aryl halides.^{4c,h} From an industrial viewpoint, the use of a copper catalyst for C–S bond formation is attractive. Traditional copper-mediated carbon–sulfur coupling requires the use of copper salts in greater than stoichiometric amounts, polar solvents such as HMPA and high temperatures (>200 °C). Furthermore, these methods lack efficiency and applicability.⁶ Of the catalytic processes reported,^{7,8} the most attractive are those of Palomo,^{8a} Venkataraman,^{8b} Buchwald and Kwong^{8c}

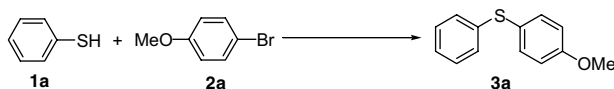
and Ma and co-workers.^{8d} Our recent results on CuI/benzotriazole catalyzed C–N bond formation encouraged us to extend our system for C–S bond formation.⁹ Thus, in continuation of our work on coupling reactions, herein, we report a general, efficient and inexpensive triazole ligand for copper-catalyzed C–S coupling.

Copper(I) complexes generally gave better results compared to copper(II) sources in terms of conversions and yield of the product. Hence, we chose CuI as the catalyst due to its stability to air. We initially assessed the catalytic activity of CuI by conducting the coupling of electron-rich 1-bromo-4-methoxybenzene **2a** with benzenethiol **1a**. Our studies show that 5 mol % of CuI and 10 mol % of benzotriazole in DMSO at 100 °C with base (1.4 equiv) were ideal conditions for formation of the desired aryl sulfide in ~90% yield in 4 h (Table 1, entry 5). However, only a trace of diaryl sulfide was observed if CuI alone was used as the catalyst (Table 1, entry 2). This indicated that benzotriazole, was essential as a ligand for the coupling reaction. Both KO^{*t*}-Bu and Cs₂CO₃ were found to be effective bases for this coupling, however, the use of other bases such as Et₃N or K₂CO₃ gave somewhat lower yields. Amongst polar solvents other than DMSO, DMF and dioxane gave similar results, see Table 1.

A literature survey revealed that coupling reactions with Cu/ligand systems occur with low turnover numbers (TON ≤ 50). Thus, in search of higher turnover numbers a series of reactions of 4-bromoanisole with thio-phenol were conducted with 4, 3, 2, 1, 0.5 and

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Table 1. Screening of reaction conditions for the copper-catalyzed C–S coupling of benzenethiol **1a** with 1-bromo-4-methoxybenzene **2a** using benzotriazole as ligand^a

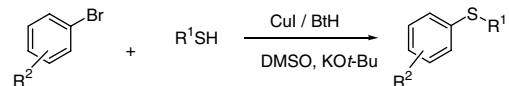
Entry	Conditions	BtH (mol %)	Yield ^b (%)
1	KO <i>t</i> -Bu, DMF, 120 °C, 24	—	nd
2	CuI (5 mol %), KO <i>t</i> -Bu, DMF, 120 °C, 10 h	—	nd
3	CuI (5 mol %), KO <i>t</i> -Bu, DMF, 100 °C, 10 h	10	91
4	CuI (5 mol %), KO <i>t</i> -Bu, dioxane, 100 °C, 10 h	10	85
5	CuI (5 mol %), KO <i>t</i> -Bu, DMSO, 100 °C, 10 h	10	94
6	CuI (4 mol %), KO <i>t</i> -Bu, DMSO, 100 °C, 10 h	8	94
7	CuI (3 mol %), KO <i>t</i> -Bu, DMSO, 100 °C, 12 h	6	95
8	CuI (2 mol %), KO <i>t</i> -Bu, DMSO, 100 °C, 12 h	4	98
9	CuI (1 mol %), KO <i>t</i> -Bu, DMSO, 100 °C, 15 h	2	98
10	CuI (0.5 mol %), KO <i>t</i> -Bu, DMSO, 100 °C, 18 h	1	98
11	CuI (0.25 mol %), KO <i>t</i> -Bu, DMSO, 100 °C, 18 h	0.5	88

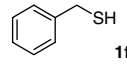
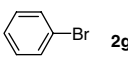
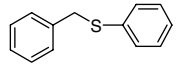
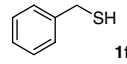
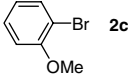
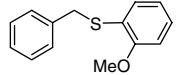
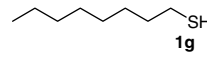
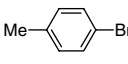
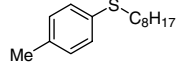
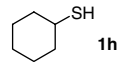
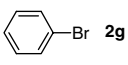
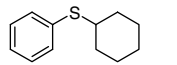
nd, not determined.

^a Reaction conditions: all reactions were performed with 1 mmol of **1a**, 1 mmol of **2a**, 1.4 mmol of KO*t*-Bu in 1 ml of solvent.^b Isolated yields (average of three runs).**Table 2.** Copper-catalyzed coupling of aryl bromides with arylthiols using benzotriazole as ligand^a

Entry	Thiols	ArX	Product	Yield ^b (%)
1	1a	2a	3a	96
2		2b	3b	95
3		2c	3c	94
4		2d	3d	98
5	1b	2e	3e	98
6		2f	3f	91 ^c
7		2b	3g	94
8	1c	2g	3h	92
9		2h	3i	89
10	1d	2e	3j	98
11		2g	3k	94
12	1e	2a	3l	93
13		2i	3m	90 ^c

^a Reaction conditions: all reactions were performed with 1 mmol of thiol, 1 mmol of ArX, 1.4 mmol of KO*t*-Bu, 0.5 mol % of CuI and 1 mol % of BtH in 1 ml of DMSO at 100 °C.¹⁰^b Isolated yields.^c Cs₂CO₃ was used as base.

Table 3. Copper-catalyzed coupling of aryl bromides with alkylthiols using benzotriazole as ligand^a


Entry	Thiol	Halide	Product	Yield ^b
1				98
2				95
3				99
4				98

^a Reaction conditions: all reactions were performed with 1 mmol of alkylthiols, 1 mmol of ArX, 1.4 mmol of KO*t*-Bu, 0.5 mol % of CuI and 1 mol % of BtH in 1 ml of DMSO at 80 °C.

^b Isolated yields.

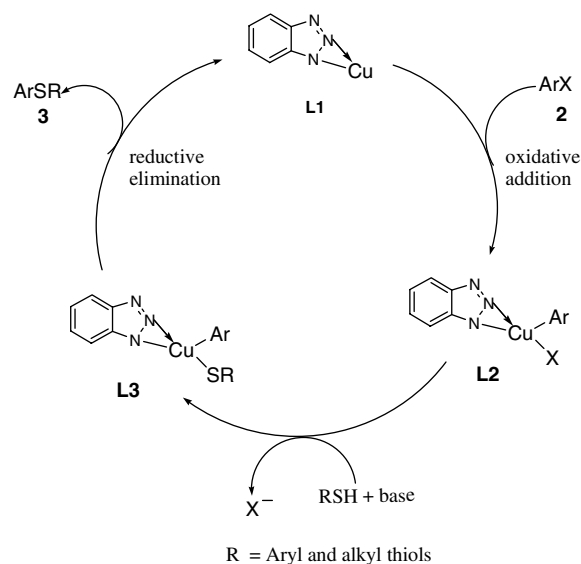
0.25 mol % of CuI and the corresponding optimized equivalent amount (8, 6, 4, 2, 1 and 0.5 mol %) of benzotriazole. We found that all combinations of CuI and ligand gave the desired product in good to excellent yields. Excellent yields in short reaction times were obtained using 0.5 mol % of CuI and 1 mol % of BtH (Table 1, entry 10).

The reactions of a series of aryl bromides and arylthiols were evaluated under these optimized conditions, and the results are summarized in Table 2.¹⁰ All the substituted arylthiols were successfully coupled with inactivated aryl bromides. The coupling of bromoarenes with thiols was tolerant of a wide range of common functional groups. Reactions of aryl bromides possessing carboxylic acid and aldehyde groups, which are incompatible with nucleophilic bases, occurred in high yields in the presence of the weaker base Cs₂CO₃.

Alkylthiols were also found to be effective nucleophiles under these reaction conditions (Table 3). Benzylmercaptan, octanethiol and cyclohexylmercaptan were all *S*-arylated in excellent yields at 80 °C.

A possible mechanism for the copper catalyzed C–S bond formation based on the previously reported mechanism is shown in Scheme 1.^{2,4,9} Chelation of Cu(I) with BtH occurs to form species **L1**, which is more reactive towards oxidative addition than stabilized intermediate **L2**⁹ generated by oxidative addition of **L1** to aryl halide. In the presence of base, aryl and alkyl thiols react with intermediate **L2** readily to afford intermediate **L3**, which undergoes reductive elimination to provide the desired product and regenerate the active Cu(I) species. Study of the actual mechanism is in progress.

In conclusion, we have developed an experimentally simple method for the mild and efficient coupling of aryl bromides and thiols. This reaction can be performed under air and without taking any precautions to exclude moisture. Our protocol is palladium free and avoids

**Scheme 1.** Possible mechanism.

the use of expensive and/or air sensitive ligands. Further studies on the scope of this reaction are currently underway in our laboratory.

Acknowledgement

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10. *Typical experimental procedure*: To a round bottomed flask containing CuI (0.5 mol%) and benzotriazole (1.0 mol%) in 1 ml of DMSO, 1 mmol of aryl halide was added and the reaction stirred for 10 min. Next, 1 mmol of arylthiol (or alkylthiol) and 1.4 equiv of KO^t-Bu were added and the reaction mixture was stirred vigorously for 10–18 h at 100 °C (80 °C for thiols). After completion of the reaction (monitored by TLC), ethyl acetate 10 mL was added and the reaction mixture was washed with water (3 × 10 mL) and combined organics dried over Na₂SO₄ and evaporated under vacuum. The residue was purified by column chromatography (hexanes) to afford the corresponding desired product. All the products have been characterized by ¹H NMR, ¹³C NMR and mass spectroscopy. **Table 2**, entry 4 (**3d**): colourless oil, ¹H NMR (300 MHz, CDCl₃): δ = 7.58–7.51 (m, 3H), 7.48–7.35 (m, 8H), 7.33–7.21 (m, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 140.3, 140.2, 139.9, 134.4, 131.2, 131.1, 129.6, 128.8, 127.8, 127.5, 127.1, 127.0; TOF-MS ES *m/z*: 261.069 (M–1). **Table 2**, entry 5 (**3e**): colourless oil, ¹H NMR (300 MHz, CDCl₃): δ = 8.42–8.39 (m, 1H), 7.51–7.39 (m, 3H), 7.26 (d, 1H, *J* = 2.7 Hz), 7.23 (s, 1H), 6.99–6.95 (m, 1H), 6.33 (dt, 1H, *J* = 0.9, 6.3 Hz), 2.39 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 162.2, 149.5, 139.4, 136.6, 135.2, 130.4, 127.2, 120.8, 119.6, 21.3; TOF-MS ES *m/z*: 202.211 (M+1). **Table 2**, entry 6 (**3f**): yellow crystals, mp = 68–70 °C ¹H NMR (300 MHz, CDCl₃): δ = 9.89 (s, 1H), 7.71–7.67 (m, 2H), 7.45–7.42 (m, 2H), 7.25 (d, 2H, *J* = 8.4 Hz), 7.18 (dd, 2H, *J* = 1.8, 5.1 Hz), 2.41 (s, 3H); ¹³C NMR (100 MHz, CDCl₃): δ = 191.1, 148.1, 139.7, 134.8, 133.4, 130.6, 130.0, 127.2, 126.5, 21.3; TOF-MS ES *m/z*: 227.132 (M–1).