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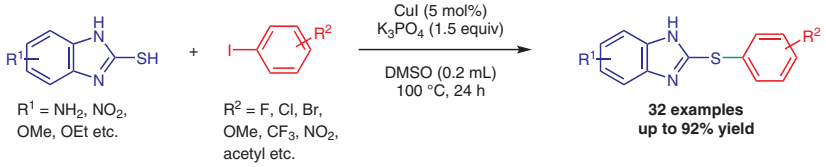
Ligand-Free CuI-Catalyzed Chemoselective S-Arylation of 2-Mercaptobenzimidazole with Aryl Iodides

Bryan Yong-Hao Tan
Yong-Chua Teo*

Natural Sciences and Science Education, National Institute of Education, Nanyang Technological University, 1 Nanyang Walk, Singapore 637616, Singapore
yongchua.teo@nie.edu.sg



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Abstract A practical and efficient strategy for the chemoselective C–S cross-coupling of 2-mercaptobenzimidazole derivatives with a range of substituted aryl iodides is described. Under the optimized conditions of 5 mol% CuI and 100 °C, a variety of S-arylated products were obtained in good to excellent yields (up to 92 %) without the need for assisting ligands.

Key words 2-mercaptobenzimidazole, ligand-free, S-arylation, copper(I) iodide, chemoselective

Transition-metal-catalyzed cross-coupling reaction has recently emerged as a powerful tool for the assembly of C–S bonds. This class of reaction had been less extensively explored relative to the C–N and C–O counterparts, mainly because of two reasons; the ability of sulfur-containing organic compounds to poison catalysts due to the sulfur's metal binding properties,[1–3] and the affinity of sulfur to form disulfide bonds.[4] Nonetheless, considerable progress has been attained ever since the first S-arylation was achieved using Pd catalyst in 1980.[5] Thereafter, various research groups have reported different methodologies to achieve S-arylation by using transition metals like Ni,[6–8] Pd,[2,3,9] and Cu[6,10–15] as catalysts. However, the above-mentioned reactions are generally applied to benzenethiol and derivatives as substrates, with little emphasis on other class of S-containing compounds. Mercaptoazoles, which are commonly found in bioactive molecules, are one of these compounds that have not been studied comprehensively.

The *S*-aryl mercaptobenzimidazole functional groups have been highlighted increasingly in pharmaceuticals and bioactive molecules. This core structure is frequently associated with anti-inflammatory,[16,17] antiviral,[18–20] antitumor,[21,22] and antibacterial[23,24] characteristics. Classically, this core structure is synthesized through the reaction of diphenyl sulfide and benzimidazoles.[25] However, this reaction has limited synthetic utility due to the low efficiency and limited substrate scope. In this context, the Ullmann-type cross-coupling provides a facile route for the synthesis of *S*-aryl mercaptobenzimidazole derivatives.[26,27] This route is advantageous due to its high catalytic efficiency, while the low cost and toxicity of the Cu catalyst further enhance the attractiveness of the method.[28–31]

While substantial development has been observed in the Ullmann-type C–S bond-formation reactions, examples which used mercaptoazoles as the S-nucleophile are still few and far between. Sambandam and co-workers employed a CuI/1,10-phenanthroline catalytic system for the cross-coupling of iodobenzene and 2-mercaptobenzimidazole.[32] While generally effective, substrate scope was limited to stabilized mercaptobenzimidazole with strong electron-donating substituents. The necessity for 1,10-phenanthroline-assisting ligand entails extra cost to the synthetic method. Braga and co-workers demonstrated the C–S cross-coupling reaction between benzenethiol and aryl iodides through the use of ionic liquid and CuO nanopowder. During his attempt to expand the generality of the reaction, he successfully coupled 2-mercaptobenzimidazole and iodobenzene to afford the intended product at a good yield of 80%. However, the use of nanoparticle and ionic liquid complicates the reaction which has very limited mercaptoazole scope. Notably, we have recently established a Cu^0-catalyzed ligand-free C–S arylation of mercaptoazole with iodobenzene, which afforded excellent yields of up to 90%.[33]

Drawing inspiration from our preceding experience in the development of sustainable and practical copper-catalyzed, ligand-free carbon-heteroatom cross-coupling reactions,[34–37] we envision the application of a ligand-free Ullmann-type cross- coupling reaction for the chemoselective C–S bond formation in 2-mercaptobenzimidazole. Hence-

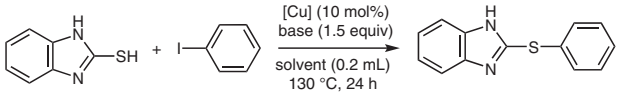
forth, a ligand-free chemoselective S-arylation of 2-mercaptobenzimidazole is disclosed. Catalyzed by CuI salt, this reaction proceeds efficiently at relatively mild temperature of 100 °C to afford good to excellent yields of up to 92% products.

The optimization studies began with the use of iodobenzene and 2-mercaptobenzimidazole as model substrates. Based on our precedent reaction,[33] Cu^0 and Cs_2CO_3were added to the reaction system, albeit at a higher reaction temperature and catalyst loading of 130 °C and 10 mol%, respectively. An encouraging yield of 60% of *S*-aryl mercaptobenzimidazole was obtained under this initial experiment (Table 1, entry 1). This was followed up with a brief study of several commercially available Cu salts as possible catalyst (Table 1, entries 2–6). The Cu halide salts were deemed to be the best catalysts for the reaction, with a slight advantage in efficiency observed for CuI. Cu^{II} salts also had potential catalytic properties for this protocol, where a moderate yield of 49% was obtained through the use of CuO. Next, a survey into the effect of different solvents had on the protocol was carried out through the use of commercially available solvents (Table 1, entries 7–11). DMSO was the best solvent, affording excellent yield of 90%. Significant decrease in product yield was observed when toluene and water was applied. The effects of base on reaction efficiency appeared to be inconsequential. This was apparent as excellent yields of 80–90% were observed during the screening reactions (Table 1, entries 12–15). K_3PO_4 was selected as the ideal base for its slightly higher yield, as well as intangibles like commercial availability and ease of handling. Negative results were detected for control reactions carried out in the absence of Cu catalyst and base, outlining their critical role in the reaction (Table 1, entries 16 and 17). To conclude the optimization studies, attempts to reduce catalyst loadings and reaction temperature were both successful, where no compensation was observed at half the initial catalyst loading and lower operating temperature of 100 °C (Table 1, entries 18 and 19). Based on these results, the optimized conditions were determined as follows: anhydrous K_3PO_4as base, DMSO as the solvent in the presence of 5 mol% CuI catalyst.

The substrate scope was studied through the application of a wide range of substituted iodobenzenes. Under optimized reaction conditions, moderate to high yields of up to 92% of the intended S-arylated compounds were obtained, as shown in Table 2. In general, this reaction was unaffected by the position and electronic nature of the substituents. Remarkably, unlike many Ullmann-type coupling reactions which gave poor results with sterically hindered *ortho*-substituted aryl halides,[38,39] this protocol was able to produce good results with these challenging substrates (Table 2, entries 2–6). Excellent yields were also observed for *meta*- and *para*-substituted iodobenzenes (Table 2, entries 7–24). Furthermore, the reaction was not limited to phenyl iodides, with naphthalene iodides also producing excellent yields of the desired products (Table 2, entries 25 and 26). However, this protocol does not apply to bromobenzene, where only trace product was obtained when applied as the aryl halide (Table 2, entry 27).

In our endeavor to expand the scope of the newly established protocol, several mercaptobenzazoles and differently substituted mercaptobenzimidazoles were applied to the catalytic system (Table 3). While 2-mercaptobenzothiazole was successfully coupled to iodobenzene, forming the *S*-aryl product in an excellent yield of 87% (Table 3, product **3a**), only trace products were detected when 2-mercaptobenzoxazole was utilized as the S-nucleophile (Table 3, product **3b**). This can be attributed to the basic property of the oxygen atom which can coordinate to the Cu catalyst and deactivate its catalytic activity. 2-Mercaptobenzimidazoles with substituents of either electron-donating or electron-withdrawing effect were well-tolerated to form

Table 1 Optimization Studies on the Cu-Catalyzed C–S Cross-Coupling of 2-Mercaptobenzimidazole and Iodobenzene[a]

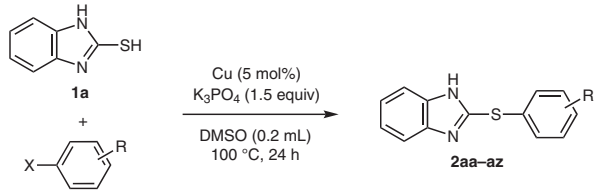


Entry	Catalyst	Base	Solvent	Yield (%)[b]
1	Cu	Cs_2CO_3	DMSO	60
2	CuI	Cs_2CO_3	DMSO	90
3	CuBr	Cs_2CO_3	DMSO	86
4	CuCl	Cs_2CO_3	DMSO	84
5	Cu_2O	Cs_2CO_3	DMSO	79
6	CuO	Cs_2CO_3	DMSO	49
7	CuI	Cs_2CO_3	DMF	86
8	CuI	Cs_2CO_3	THF	75
9	CuI	Cs_2CO_3	*t*-BuOH	67
10	CuI	Cs_2CO_3	toluene	38
11	CuI	Cs_2CO_3	water	39
12	CuI	K_2CO_3	DMSO	83
13	CuI	K_3PO_4	DMSO	90
14	CuI	KOH	DMSO	80
15	CuI	CsOAc	DMSO	80
16	–	K_3PO_4	DMSO	0
17	CuI	–	DMSO	0
18	CuI	K_3PO_4	DMSO	90[c]
19	CuI	K_3PO_4	DMSO	90[c,d]

[a] Reaction conditions: Cu catalyst (10 mol%), base (0.75 mmol), 2-mercaptobenzimidazole (0.50 mmol), solvent (0.2 ml), iodobenzene (0.75 mmol), 130 °C for 24 h in air.
[b] Isolated yield.
[c] 5 mol% CuI used.
[d] Reaction carried out at 100 °C.

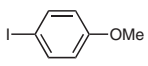
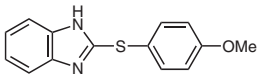
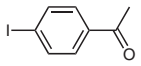
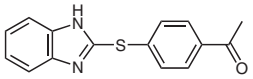
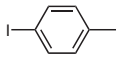
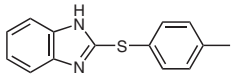
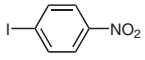
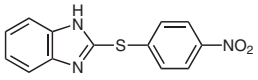
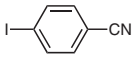
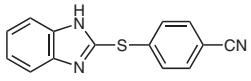
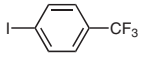
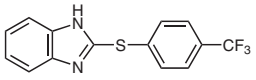
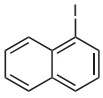
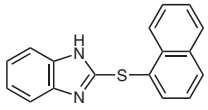
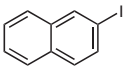
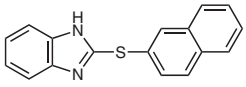
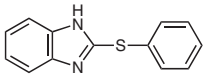
the corresponding products in good to excellent yields of up to 85% (Table 3, products **3b–g**). The cross-coupling of N-protected 2-mercaptobenzimidazole was also complete, where an excellent yield of 87% was observed (Table 3, product **3h**). This evidence supports the fact that arylation indeed is favored at the sulfur atom rather than the nitrogen atom.

Table 2 Chemoselective S-Arylation of 2-Mercaptobenzimidazole with Various Substituted Aryl Halides[a]



Entry	ArX	Product	Yield (%)[b]
1	**2a**	**2aa**	90
2	**2b**	**2ab**	86
3	**2c**	**2ac**	88
4	**2d**	**2ad**	83
5	**2e**	**2ae**	84
6	**2f**	**2af**	82
7	**2g**	**2ag**	86
8	**2h**	**2ah**	84
9	**2i**	**2ai**	85
10	**2j**	**2aj**	84
11	**2k**	**2ak**	92
12	**2l**	**2al**	87
13	**2m**	**2am**	83
14	**2n**	**2an**	83
15	**2o**	**2ao**	85
16	**2p**	**2ap**	92
17	**2q**	**2aq**	85
18	**2r**	**2ar**	83

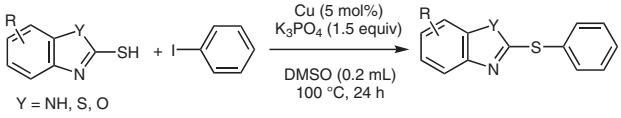
Table 2 (continued)

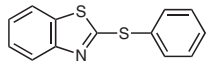
Entry	ArX	Product	Yield (%)[b]
19	 **2s**	 **2as**	84
20	 **2t**	 **2at**	90
21	 **2u**	 **2au**	86
22	 **2v**	 **2av**	72
23	 **2w**	 **2aw**	71
24	 **2x**	 **2ax**	86
25	 **2y**	 **2ay**	90
26	 **2z**	 **2az**	92
27	 **2a'**	 **2aa**	trace

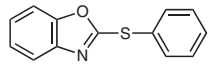
[a] Reactions were carried out with CuI (5 mol%), K_3PO_4 (0.75 mmol), 2-mercaptobenzimidzole (0.50 mmol), DMSO (0.2 ml), substituted iodobenzene (0.75 mmol), 100 °C for 24 h in air.
[b] Isolated yield.

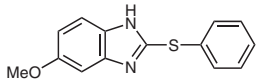
In conclusion, an efficient ligand-free CuI catalytic system for the Ullmann-type S-arylation of 2-mercaptobenzimidazoles[40] is described. A good range of mercaptobenzazole and substituted mercaptobenzimidazole were found to react with iodobenzene in the presence of 5 mol% CuI in DMSO. The corresponding S-arylated products were obtained in up to 92% yield. This protocol is general and mild, and the use of inexpensive and commercially available CuI catalyst without the need for expensive ligands or stringent inert conditions makes it a feasible alternative to established C–S cross-coupling methodologies.

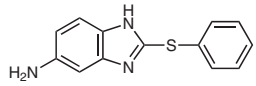
Table 3 Chemoselective *S*-Arylation of 2-Mercaptobenzimidazole Derivatives with Iodobenzene[a]

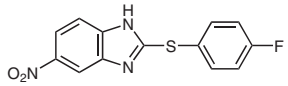


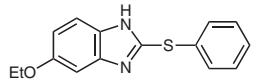

3a, 87% yield

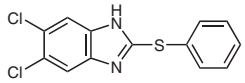

3b, trace

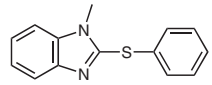

3c, 82% yield


3d, 66% yield


3e, 77% yield


3f, 84% yield


3g, 85% yield


3h, 87% yield

[a] Isolated yields for reactions carried out with Cu (5 mol%), K_3PO_4 (0.75 mmol), 2-mercaptoimidazole derivatives (0.50 mmol), DMSO (0.2 ml), iodobenzene (0.75 mmol), 100 °C for 24 h in air.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610655.

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(40) **General Procedure for S-Arylation of 2-Mercaptobenzimidazoles**

A mixture of CuI (Sigma-Aldrich, 0.025 mmol, 5 mol%), anhydrous K_3PO_4 (0.65 mmol), 2-mercaptobenzimidazole (0.5 mmol), DMSO (0.2 mL), and aryl halide (0.75 mmol) were added to a reaction vial and a screw cap was fitted to it. The reaction mixture was stirred under air in a closed system at 100 °C for 24 h. The heterogeneous mixture was subsequently cooled to room temperature and diluted with dichloromethane. The combined organic extracts were dried with anhydrous Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was loaded into the column using minimal amounts of dichloromethane and was purified by silica gel column chromatography to afford the S-arylated product. The identity and purity of products was confirmed by ^{1}H NMR and ^{13}C NMR spectroscopic analysis.

2-(Phenylthio)-1*H*-benzo[*d*]imidazole (2aa)

101 mg (90% yield) of the coupled product was obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d): δ = 12.50 (br s, 1 H), 7.62 (dd, J = 25.6, 7.6 Hz, 2 H), 7.42–7.31 (m, 7 H). ^{13}C NMR (100 MHz, DMSO-d): δ = 147.6, 135.4, 131.3, 130.1, 129.6, 122.8, 118.7, 110.4. HRMS: *m/z* calcd [M$^+$]: 227.0641; found: 227.0644.

2-[(2-Fluorophenyl)thio]-1*H*-benzo[*d*]imidazole (2ab)

105 mg (86% yield) of the coupled product was obtained as an off-white solid.
^{1}H NMR (400 MHz, DMSO-d): δ = 12.77 (br s, 1 H), 7.58–7.48 (m, 3 H), 7.42–7.35 (m, 2 H), 7.28 (t, J = 5.6 Hz, 1 H), 7.16 (m, 2 H). ^{13}C NMR (100 MHz, DMSO-d): δ = 160.8 (d, J = 240.0 Hz), 144.7 (d, J = 220.0 Hz), 134.7, 131.4 (d, J = 3.0 Hz), 125.5 (d, J = 3.0 Hz), 122.4, 119.8 (d, J = 340.0 Hz), 116.4, 116.2, 110.9. HRMS: *m/z* calcd [M$^+$]: 245.0546; found: 245.0547.

2-[(2-Chlorophenyl)thio]-1*H*-benzo[*d*]imidazole (2ac)

114 mg (88% yield) of the coupled product was obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d): δ = 12.96 (br s, 1 H), 7.60 (dd, J = 7.6, 1.6 Hz, 3 H), 7.40–7.29 (m, 3 H), 7.21 (s, 2 H). ^{13}C NMR (100 MHz, DMSO-d): δ = 144.4, 133.1, 131.9, 131.3, 130.0, 129.4, 128.2, 122.7, 118.5, 111.3. HRMS: *m/z* calcd [M$^+$]: 261.0251; found: 261.0249.

2-[(2-Methoxyphenyl)thio]-1*H*-benzo[*d*]imidazole (2ad)

106 mg (83% yield) of the coupled product was obtained as an off-white solid. ^{1}H NMR (400 MHz, DMSO-d): δ = 12.64 (br s, 1 H), 7.49 (s, 2 H), 7.36 (t, J = 7.6 Hz, 2 H), 7.24–7.11 (m, 3 H), 6.96 (t, J = 7.6 Hz, 1 H), 3.82 (s, 3 H). ^{13}C NMR (100 MHz, DMSO-d): δ = 157.1, 146.3, 131.8, 129.7, 121.9, 121.3, 119.3, 111.9, 106.1, 56.0. HRMS: *m/z* calcd [M$^+$]: 257.0746; found: 257.0743.