

Efficient Copper(I)-Catalyzed C–S Cross Coupling of Thiols with Aryl Halides in Water

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CuI efficiently catalyzes the C–S cross coupling of thiols with aryl halides in the presence of tetrabutylammonium bromide in water. The reactions with aryl thiols that have electron-withdrawing and -donating substituents are comparable and afford C–S cross-coupling products in high yield.

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Introduction

The formation of C–S bonds is a powerful means for the preparation of numerous compounds of biological and pharmaceutical interest and for use in the material sciences.^[1] The traditional methods available for this purpose, however, often require harsh reaction conditions – the use of polar solvents such as HMPA, high temperatures around 200 °C, and the reduction of sulfones or sulfoxides with strong reducing agents such as DIBAL-H or LiAlH₄.^[2] To overcome these drawbacks, considerable attention has recently been focused on the development of catalytic systems for the cross coupling of thiols with aryl halides. In 1980, Migita and co-workers first reported the cross coupling of aryl halides with thiols in the presence of [Pd(PPh₃)₄] as the catalyst and NaO^tBu as the base, in polar solvents such as ethanol heated at reflux or dimethyl sulfoxide (DMSO) at 90 °C.^[3] Palladium-,^[4] nickel-,^[5] copper-,^[6] and cobalt-based^[7] catalytic systems have since been studied for this purpose. These reactions are effective in anhydrous solvents under inert conditions.

The use of water as a solvent for organic reactions has been extensive in recent years.^[8,9] Because water is cheap, nontoxic, safe, and environmentally benign relative to organic solvents. Herein we report that CuI efficiently catalyzes the C–S cross coupling of thiols with aryl halides in the presence of tetrabutylammonium bromide (TBAB) in water. These reactions are effective in air in the presence of KOH at moderate temperature. During this study, Carril et

al. reported the formation of thioethers by using copper salts and 1,2-diamine derivatives in water.^[6n]

Results and Discussion

First, we studied the cross coupling of thiophenol with iodobenzene as the model substrate (Table 1). The reaction afforded the desired C–S cross-coupling diphenylsulfide in 98% yield when the substrate was stirred in water at 80 °C for 10 h in the presence of 1 mol-% CuI, 1.1 equiv. iodobenzene, 1.5 equiv. KOH, and 1 equiv. TBAB in air. Among the bases studied – KOH, K₂CO₃, Cs₂CO₃, pyridine, and DIPA (diisopropylamine) – the first provided the best result. Of the copper catalysts investigated, CuI was superior to CuSO₄·5H₂O, Cu(OAc)₂·2H₂O, CuCl₂·2H₂O, Cu(NO₃)₂·3H₂O, and CuO. Iodobenzene was more reactive than bromo- and chlorobenzene. The presence of TBAB is essential and in its absence no reaction was observed.

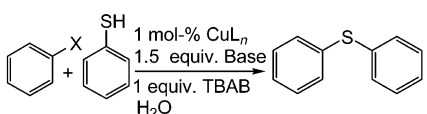
To study the scope of the procedure, the reactions of other thiols with iodobenzene were then studied (Table 2). The reactions with 2-methyl-, 4-methyl-, 4-nitro-, 2-bromo-, 4-bromo-, 4-chloro-, and 4-methoxybenzenethiol afforded cross-coupling products in 91–99% yield in 9–15 h. Similar results were observed with 2-naphthalenethiol and phenylmethanethiol; however, 1-butanethiol was less reactive, and the C–S cross-coupling product was obtained in 15% yield.

These reaction conditions are also suitable for the C–S cross coupling of thiols with chloro- and bromobenzene (Table 3). For example, the reactions with 4-methoxy-, 4-methyl-, and 4-nitrobenzenethiol afforded cross-coupling products in 30–60% yield in 14–15 h. Similar results were obtained with 2-naphthalenethiol and phenylmethanethiol – the C–S cross-coupling products were obtained in 21–48% yield in 18–19 h. Bromobenzene was more reactive than chlorobenzene.

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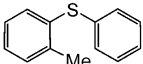
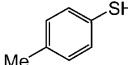
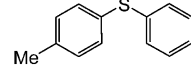
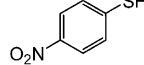
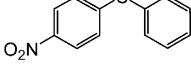
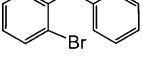
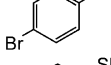
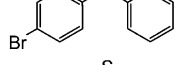
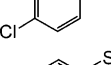
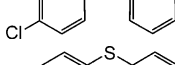
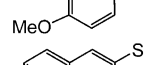
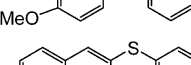
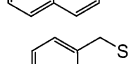
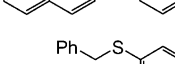
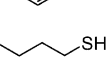
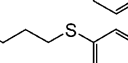
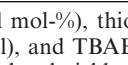
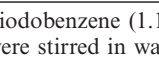
Table 1. Cross coupling of thiophenol with aryl halides in water.



Catalyst	X	Base	T [°C]	Time [h]	Yield [%] ^[a,b]
CuCl ₂ ·2H ₂ O	I	KOH	80	10	90
CuSO ₄ ·5H ₂ O	I	KOH	80	10	76
Cu(OAc) ₂ ·H ₂ O	I	KOH	80	10	88
CuO	I	KOH	80	10	72
Cu(NO ₃) ₂ ·3H ₂ O	I	KOH	80	10	85
CuI	I	KOH	80	10	98
CuI	I	KOH	r.t.	12	no reaction
CuI	I	K ₂ CO ₃	80	10	75
CuI	I	Cs ₂ CO ₃	80	10	88
CuI	I	DIPA	80	8	65
CuI	I	pyridine	80	8	75
CuI	Br	KOH	80	12	52 ^[c]
CuI	Cl	KOH	80	12	32 ^[c]

[a] The catalyst (1 mol-%), thiophenol (1 mmol), aryl halide (1.1 mmol), base (1.5 mmol), and TBAB (1 mmol) were stirred in water (1 mL) in air. [b] Isolated yield. [c] 5 mol-% catalyst used.

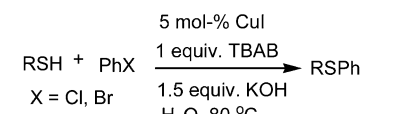
Table 2. The reaction of various thiols with iodobenzene in water.

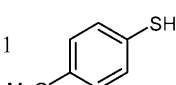
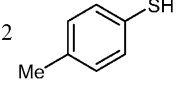
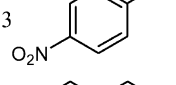
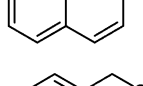
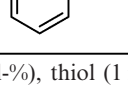
Entry	Thiol	Time [h]	Product	Yield [%] ^[a,b]
1		9		98
2		9		99
3		15		91
4		10		96
5		11		95
6		9		94
7		9.5		99
8		10		99
9		11		91
10		15		15

[a] CuI (1 mol-%), thiol (1 mmol), iodobenzene (1.1 mmol), KOH (1.5 mmol), and TBAB (1 mmol) were stirred in water at 80 °C in air. [b] Isolated yield.

Finally, the reactions of thiophenol with aryl iodides that have electron-donating and -withdrawing substituents were investigated (Table 4). The reaction with 1-iodo-4-nitroben-

Table 3. Reaction of thiols with chloro- and bromobenzene.

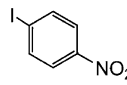
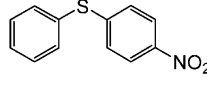
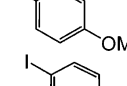
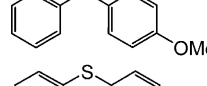
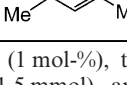
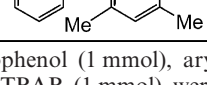


Entry	RSH	X	Time [h]	RSPH [%] ^[a,b]
1		Cl	15	45
		Br	15	60
2		Cl	14	39
		Br	14	50
3		Cl	15	30
		Br	15	41
4		Cl	18	30
		Br	18	48
5		Cl	19	21
		Br	19	32

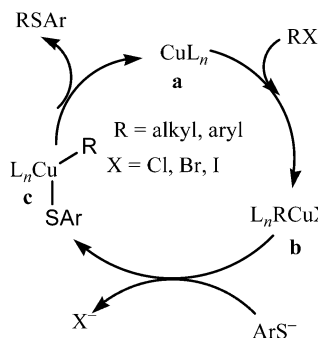
[a] CuI (5 mol-%), thiol (1 mmol), iodobenzene (1.1 mmol), KOH (1.5 mmol), and TBAB (1 mmol) were stirred in water at 80 °C in air. [b] Isolated yield.

zene afforded the product in a 95% yield in 6 h, while the reactions of 1-iodo-4-methoxybenzene and 1-iodo-2,4-dimethylbenzene required 12 h to provide the cross-coupling products in 75% and 85% yield, respectively. These results suggest that the reaction occurs by oxidative addition followed by reductive elimination (Scheme 1). The oxidative addition of the aryl halide with catalyst **a** can give intermediate **b**, which can undergo reaction with a thiol to afford intermediate **c**. Intermediate **c** can provide the C–S cross-coupling product by reductive elimination, where TBAB presumably acts as the phase-transfer catalyst, solubilizing the organic substrates in water.^[9]

Table 4. The cross coupling of thiols with substituted aryl iodides.

Entry	Aryl iodide	Product	Time [h]	Yield [%] ^[a,b]
1			6	95
2			12	75
3			12	85

[a] CuI (1 mol-%), thiophenol (1 mmol), aryl iodide (1.1 mmol), KOH (1.5 mmol), and TBAB (1 mmol) were stirred at 80 °C in water (1 mL) in air. [b] Isolated yield.



Scheme 1. Proposed catalytic cycle.

Conclusions

In conclusion, a simple and efficient procedure is described for C–S bond formation by cross coupling of thiols with aryl halides by using a combination of CuI and TBAB in water. These reactions do not require an inert atmosphere and can be performed at moderate temperatures with high yields.

Experimental Section

Materials and Methods: Thiols, bromobenzene (99%), chlorobenzene (99%), iodobenzene (98%), CuCl₂·2H₂O (99%), CuSO₄·5H₂O (98%), Cu(OAc)₂·H₂O (99%), CuO (99.99%), Cu(NO₃)₂·3H₂O (98%), and CuI (99.99%) were purchased from Aldrich. NMR spectra (400 MHz for ¹H and 100 MHz for ¹³C) were recorded with a DRX-400 Varian spectrometer by using CDCl₃ as solvent and Me₄Si as internal standard. Flash column chromatography was performed on silica gel (230–400 mesh) with ethyl acetate and hexane as eluent. Melting points were determined by using a Büchi B-540 melting point apparatus and are uncorrected.

General Procedure for the C–S Cross-Coupling Reaction: CuI (1 mol-%) was added to a stirred solution of thiol (1 mmol), aryl halide (1.1 mmol), TBAB (1 mmol), and KOH (1.5 mmol) in water (1 mL). The solution was heated at 80 °C in air for the appropriate time. The progress of the reaction was monitored by TLC. The reaction mixture was then cooled to room temperature and treated with diethyl ether (10 mL). The aqueous layer was separated and extracted with diethyl ether (3 × 5 mL). The combined organic solution was successively washed with brine (3 × 5 mL) and water (1 × 5 mL), dried (Na₂SO₄), and passed through a short pad of silica gel by using ethyl acetate and hexane as eluent to afford analytically pure cross-coupling products.

Supporting Information (see footnote on the first page of this article): ¹H and ¹³C NMR data and spectra of all the C–S cross-coupled products.

Acknowledgments

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