

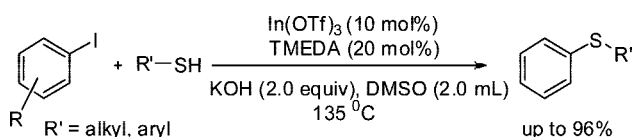
Indium-Catalyzed C–S Cross-Coupling of Aryl Halides with Thiols

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Indium-catalyzed C–S cross-coupling of aromatic and alkane thiols with aryl halides proceeds smoothly in the presence of In(OTf)₃ (10 mol %), TMEDA (20 mol %), and KOH as a base in DMSO at 135 °C. When this protocol was utilized, a variety of thiols could be cross-coupled with aryl halides to afford the corresponding aryl sulfides in good to excellent yields.

Aryl sulfides are an important class of organic compounds found in numerous pharmaceutically active compounds¹ as well as in a number of drugs in therapeutic areas, such as diabetes, inflammatory, immune, Alzheimer's, and Parkinson's diseases.² In the past decade, palladium-,³ nickel-,⁴ copper-,⁵ and cobalt-based⁶ catalytic systems have been studied for this purpose. Recently, Bolm et al. reported the first genuine iron-catalyzed

TABLE 1. Indium-Catalyzed C–S Cross-Coupling of Thiophenol with Iodobenzene^a

entry	base	solvent	yield ^b (%)
1	Cs ₂ CO ₃	DMSO	72
2	K ₃ PO ₄	DMSO	trace
3	NaOMe	DMSO	0
4	KOH	DMSO	96
5	KOH	toluene	trace
6	KOH	DMF	trace

^a Reaction conditions: thiophenol (1.0 mmol), iodobenzene (1.1 mmol), In(OTf)₃ (10 mol %)/ligand (20 mol %), base (2.0 equiv), solvent (2.0 mL), 135 °C, 24 h. ^b Yield of isolated product after flash chromatography.

C–S cross-coupling;⁷ however, this protocol was ineffective when using aliphatic thiols for C–S coupling. Therefore, the iron-catalyzed C–S cross-coupling reaction needs to be modified to expand the scope of these methodologies and to employ more universal ligands.

In this study, we report an efficient indium-catalyzed C–S cross-coupling of aryl halides with various aliphatic and aromatic thiols using *N,N,N',N'*-tetramethylethylenediamine (TMEDA) as the ligand. In the first instance, we have studied the cross-coupling of iodobenzene (1) with thiophenol (2) as the model reaction in the presence of In(OTf)₃ (10 mol %)/TMEDA (20 mol %) and KOH in DMSO at 135 °C for 24 h, and the corresponding aryl sulfide (3) was obtained in 96% yield (Table 1, entry 4). To the best of our knowledge, this is the first In(OTf)₃-catalyzed cross-coupling of aryl halides with thiols to form aryl sulfides.

To optimize the reaction conditions, we have made a study about the effect of different solvents and bases on the C–S cross-coupling reaction catalyzed by In(OTf)₃. The results are shown in Table 1 (entries 1–6). Among these solvents, DMSO was found to be most efficient. In a comparison of the efficiency of the base, KOH was found to act as an excellent base, whereas Cs₂CO₃ was effective to some extent and other bases, such as K₃PO₄ and NaOMe, were not at all effective.

Next, we investigated the effect of different combinations of Lewis acids and a series of ligands on the course of the reaction, and the results are shown in Table 2 (entries 1–16).

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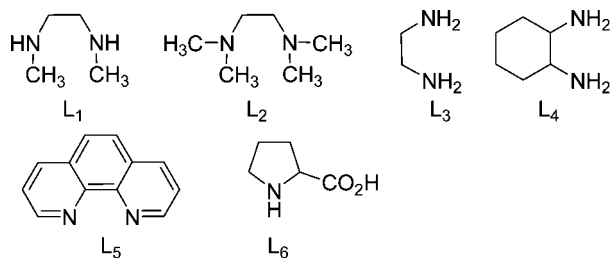
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TABLE 2. Indium-Catalyzed C–S Cross-Coupling of Thiophenol with Iodobenzene^a

entry	catalyst	ligand	yield ^b (%)
1	In	L ₂	trace
2	InCl ₃	L ₂	85
3	InBr ₃	L ₂	91
4	In(OTf) ₃	L ₁	84
5	In(OTf) ₃	L ₂	96
6	In(OTf) ₃	L ₃	59
7	In(OTf) ₃	L ₄	73
8	In(OTf) ₃	L ₅	89
9	In(OTf) ₃	L ₆	78
10	Bi(OTf) ₃	L ₂	80
11	La(OTf) ₃	L ₂	82
12	Sc(OTf) ₃	L ₂	90
13	Zn(OTf) ₂	L ₂	90
14	In(OTf) ₃		35 ^c
15		L ₂	26 ^d
16			0 ^e

^a Reaction conditions: thiophenol (1.0 mmol), iodobenzene (1.1 mmol), catalyst (10 mol %)/ligand (20 mol %), base (2.0 equiv), solvent (2.0 mL), 135 °C, 24 h. ^b Yield of isolated product after flash chromatography. ^c In the absence of ligand. ^d In the absence of catalyst. ^e In the presence of base only.



It was found that In(OTf)₃ has shown the best activity compared to other Lewis acids such as InCl₃ (85%), InBr₃ (91%), Bi(OTf)₃ (80%), La(OTf)₃ (82%), Sc(OTf)₃ (90%), and Zn(OTf)₂ (90%) with the combination of TMEDA (**L2**), which proved to be the best choice compared with the other ligands (**L1** and **L3–L6**). In the absence of any supporting ligand, the desired cross-coupling product was obtained in low yields (Table 2, entry 14). Similarly, low yields were obtained in the absence of catalyst (Table 2, entry 15). The importance of the catalyst and ligand was revealed by a reaction carried out in the presence of base alone that gave no C–S coupling product and only diphenyl disulfide (Table 2, entry 16).

To explore the scope of the reaction, various aryl halides were reacted with different substituted aromatic thiols and aliphatic thiols (Table 3). In general, all reactions were very clean and the diaryl sulfide derivatives were obtained in high yields under optimized conditions. The results have shown that substitution played a major role in governing the reactivity of the substrate. With electron-donating substituents in the aryl iodide, decreased yields of products were observed (Table 3, entries 4–6). For example, the coupling of *p*-methoxyiodobenzene with benzenethiol gave only a trace amount of the product. However, the effect was reversed when the electron-donating groups were present in thiols, and the corresponding aryl sulfides were obtained in excellent yields (Table 3, entries 7–9). Electron-withdrawing groups (e.g., CF₃, F, NO₂) in the aryl iodide favored the coupling reaction with aryl thiols, affording the corresponding thioethers in high yields (Table 3, entries 11–13). Under the same reaction conditions, 4-iodophenol and 4-iodoaniline also reacted well to give the corresponding aryl sulfides in excellent yields (Table 3, entries 14 and 15). Another important

TABLE 3. C–S Cross-Coupling of Aryl Halides with Thiols^a

entry	aryl iodide	thiol	product ^b	yield ^c (%)
1		X = I HS-Ph		96
2		Br		58
3		Cl		10
4		HS-Ph		79
5		HS-Ph		72
6		HS-Ph		15
7		HS-Ph		83
8		HS-Ph		90
9		HS-4-Me-C ₆ H ₄ -SH		94
10		HS-4-OMe-C ₆ H ₄ -SH		91
11		HS-Ph		85
12		HS-Ph		87
13		HS-Ph		81
14		HS-Ph		87
15		HS-Ph		84
16		HS-Ph		92
17		HS-Ph		75
18		C ₁₀ H ₂₁ SH		81
19		C ₅ H ₁₁ SH		85
20		C ₆ H ₁₃ SH		83
21		C ₆ H ₁₃ SH		88
22		C ₁₀ H ₂₁ SH		85
23		C ₅ H ₁₁ SH		51
24		Cyclohexyl-SH		88
25		Cyclohexyl-SH		85

^a Reaction conditions: thiophenol (1.0 mmol), iodobenzene (1.1 mmol), 0.1 equiv of In(OTf)₃, 0.2 equiv of TMEDA, 2.0 equiv of KOH, DMSO (2.0 mL), 135 °C, 24 h, nitrogen atmosphere. ^b The products were characterized by IR, ¹H and ¹³C NMR, and mass spectroscopy. ^c Yield of isolated product after flash chromatography.

aspect of the cross-coupling is the successful reaction of 3-iodopyridine and 3-bromopyridine with benzenethiol to give

good yields of the heterocyclic aryl sulfide (Table 3, entry 17).⁸ In the reaction of substrates with alkyl thiols, increasing the size of the alkyl chain led to a slight decrease in the yield of the aryl sulfides (Table 3, entries 19–22). Unfortunately, all attempts to couple benzyl thiols and heteroaromatic thiols with iodobenzene have failed.⁸

In conclusion, we have developed a novel indium-catalyzed C–S cross-coupling. The cross-coupling of aliphatic and aromatic thiols with aryl iodides and aryl bromides generates the corresponding coupling products in good to excellent yields.

Experimental Section

General Procedure. To a stirred solution of **1** (1.1 mmol) and In(OTf)₃ (10 mol %) in dry DMSO (2.0 mL) was added **2** (1.0 mmol) followed by TMEDA (20 mol %) and KOH (2.0 equiv)

under a nitrogen atmosphere. The reaction mixture was then stirred at 135 °C for 24 h. The progress of the reaction was monitored by TLC. The mixture was allowed to cool to room temperature. Diethyl ether (5 mL) was added, and the organic phase was separated, dried over anhydrous Na₂SO₄, and purified by chromatography on silica gel to afford the corresponding coupling product (**3**) in 96% yield: colorless oil, ¹H NMR (200 MHz, CDCl₃, TMS) δ 7.34–7.14 (m, 10H); ¹³C NMR (100 MHz, CDCl₃, TMS) δ 135.7, 131.0, 129.1, 127.0. The spectral data are consistent with those reported in the literature.⁶

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Supporting Information Available: Detailed experimental procedures and compound characterization data for all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(8) See the Supporting Information.

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