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Nano Indium Oxide as a Recyclable Catalyst for C−S Cross-Coupling of Thiols with Aryl Halides under Ligand Free conditions

Vutukuri Prakash Reddy, Akkilagunta Vijay Kumar, Kokkirala Swapna, and Kakulapati Rama Rao*

Organic Chemistry Division-I, Indian Institute of Chemical Technology,
Hyderabad-500 007, India

kakulapatirama@gmail.com

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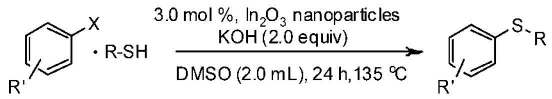
ABSTRACT



An efficient ligand-free C−S cross-coupling of aryl halides with aromatic/alkyl thiols has been developed using a catalytic amount of nanocrystalline indium oxide as a recyclable catalyst with KOH as the base in DMSO at 135 °C. A variety of aryl sulfides can be synthesized in excellent yields utilizing this protocol.

Transition-metal-catalyzed C−S bond formation has been a subject of intense study over the past decade due to the importance of aryl sulfides and their derivatives in numerous biological and pharmaceutically active compounds.[1]Indeed, a number of drugs in therapeutic areas such as diabetes, inflammatory, Alzheimer's, Parkinson's,[2] cancer,[3] and HIV[4] diseases contain the aryl sulfide functional group.

However, the transition-metal-catalyzed C−S cross-coupling reaction is much less studied than the corresponding C−N and C−O bonds, due to deactivation of the metal catalysts by the organosulfur compounds because of their strong coordinating properties.[5] This limitation led to increased interest in the field of transition metal-catalyzed organosulfur chemistry, bringing important progress in the field.

The traditional methods for C−S bond formation were of limited use due to their harsh reaction conditions. For example, the coupling of copper thiolates with aryl halides takes place in polar solvents, such as HMPA and at elevated temperatures around 200 °C. The reduction of sulfones or sulfoxides requires strong reducing agents, such as DIBAL-H or $LiAlH_4$.[6] To overcome these difficulties, transition metal-catalyzed coupling systems involving the use of palladium,[7] nickel,[8] copper,[9] and iron[10] based catalytic systems have been studied. A cobalt-catalyzed reaction in the presence of a

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(6) (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (b) Yamamoto, T.; Sekine, Y. *Can. J. Chem.* **1984**, *62*, 1544. (c) Hickman, R. J. S.; Christie, B. J.; Guy, R. W.; White, T. *J. Aust. J. Chem.* **1985**, *38*, 899. (d) Bierbeek, A. V.; Gingras, M. *Tetrahedron Lett.* **1998**, *39*, 6283.

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Table 1. Cross-Coupling of Thiophenol with Aryl Iodide[a]

entry	base	solvent	temp (°C)	yield[b] (%)
1	K_3PO_4	DMSO	135	trace
2	Cs_2CO_3	DMSO	135	69
3	KO^tBu	DMSO	135	trace
4	**KOH**	**DMSO**	**135**	**97**
5	KOH	DMSO	80	78
6	KOH	DMSO	rt	0
7	NaOMe	DMSO	135	trace
8	K_3PO_4	DMF	135	0
9	Cs_2CO_3	PhMe	135	0
10	KO^tBu	PhMe	135	0
11	KOH	PhMe	135	trace
12	KOH	DMF	135	trace
13	Cs_2CO_3	DMF	135	trace
14	KOH	Water	135	0
15	none	DMSO	135	0

[a] Reaction conditions: Iodobenzene (1.1 mmol), benzenethiol (1.0 mmol) In_2O_3 (3.0 mol %), base (2.0 equiv), solvent (2.0 mL), 24 h, under a nitrogen atmosphere. [b] Isolated yield.

ligand, CoI_2(dppe), and Zn has also been reported recently.[11] However, almost all of these methods involve ligands or well-defined catalysts and these protocols have common problems such as metal toxicity, low turnover numbers, excess reagents and nonrecyclability of these catalysts, thus increasing the cost and limiting the scope of the reaction. Recently Koten and co-workers reported copper-catalyzed C−S coupling of aryl iodides and thiols under ligand free conditions. However, this protocol reports a lone example of aliphatic thiol, butanethiol, in lower yields (54%) and also the catalyst cannot be recycled.[12] In this regard we envisaged the application of readily available and inexpensive nanoparticles as catalysts.

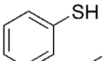
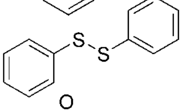
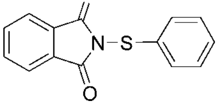
Table 2. Indium Oxide Amount Screening for the C−S Coupling[a]

entry	In_2O_3 (mol %)	yield[b] (%)
1	1.0	67
2	2.0	80
3	2.5	88
4	3.0	97
5	3.5	97

[a] Reaction conditions: Iodobenzene (1.1 mmol), benzenethiol (1.0 mmol), In_2O_3 (mol%), KOH (2.0 equiv), DMSO (2.0 mL), 135 °C, 24 h. [b] Isolated yield. [c] Sulfur source (0.5 mmol).

Over the past decades, Pd, Cu, Ni, and Fe based catalysts were explored for cross-coupling reactions. However until now there has been no report on indium catalyzed cross-coupling reaction. We attempted C−S cross-coupling with indium. Recently, nanoparticles have been employed as heterogeneous catalysts for various organic transformations.[9k,13] This inspired us to focus on the aspect of indium oxide nanoparticle catalysis for the formation of aryl−sulfur bonds. The heterogeneous catalysts are also attractive both from economic and industrial points of view as compared to homogeneous catalysts. In general, nanoscale heterogeneous catalysts offer higher surface area and lower-coordinating sites, which are responsible for the higher catalytic activity.[14] However, until now, the investigation of nanoparticles as catalysts has been scarce.

Table 3. Nano In_2O_3 Catalyzed C−S Cross-Coupling of Iodobenzene with Different Sulfur Sources[a]

entry	sulfur source	time(h)	yields[b](%)
1		24	97
2		24	60[c]
3		24	88

[a] Reaction conditions: Iodobenzene (1.1 mmol), sulfur source (1.0 mmol), In_2O_3 (3.0 mol %), KOH (2.0 equiv), DMSO (2.0 mL), 135 °C, 24 h. [b] Isolated yield. [c] Phenyl disulfide (0.5 mmol).

Initially, the reaction between iodobenzene and benzenethiol was selected as a model reaction, and various

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(9) (a) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (c) Wu, Y.-J.; He, H. *Synlett.* **2003**, 1789. (d) Bates, C. G.; Saejueng, P.; Doherty, M. Q.; Venkataraman, D. *Org. Lett.* **2004**, *6*, 5005. (e) Palomo, C.; Oiarbide, M.; Lopez, R.; Gomez- Bengoa, E. *Tetrahedron Lett.* **2000**, *41*, 1283. (f) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309. (g) Herradura, P. S.; Pendola, K. A; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019. (h) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609. (i) Ranu, B. C.; Saha, A.; Jana, R. *Adv. Synth. Catal.* **2007**, *349*, 2690. (j) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (k) Rout, L.; Sen, T. K.; Punniyamurthy, T. *Angew. Chem., Int. Ed.* **2007**, *46*, 5583.

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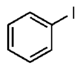
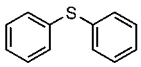
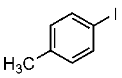
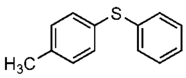
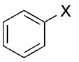
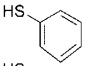
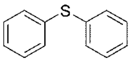
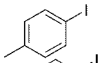
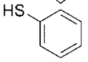
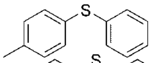
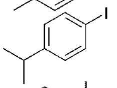
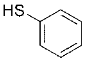
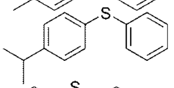
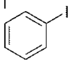
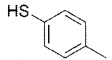
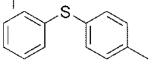
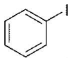
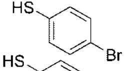
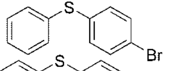
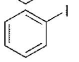
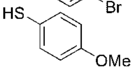
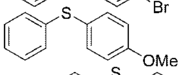
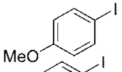
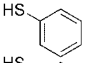
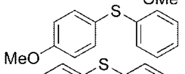
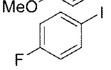
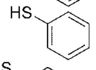
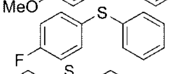
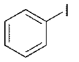
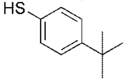
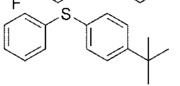
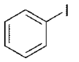
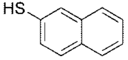
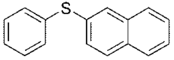
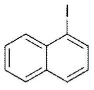
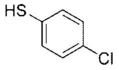
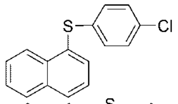
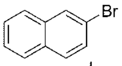
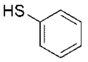
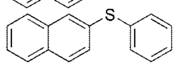
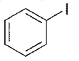
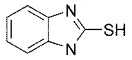
Table 4. Evaluation of Different Catalysts for the Formation of Aryl Sulfides[a]

entry	halide	product	catalyst	yield[b] (%)
1			nano-ZnO	89
2			nano-Bi_2O_3	85
3			nano-In_2O_3	97
4			nano-Sb_2O_3	89
5			nano-Co_3O_4	90
6			-	0
7			nano-ZnO	76
8			nano-Bi_2O_3	69
9			nano-In_2O_3	87
10			nano-Sb_2O_3	79
11			nano-Co_3O_4	81

[a] Reaction conditions: Iodobenzene (1.1 mmol), benzenethiol (1.0 mmol) catalyst (3.0 mol %), KOH (2.0 equiv), DMSO (2.0 mL), 135 °C, 24 h, under a nitrogen atmosphere. [b] Isolated yield.

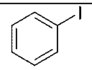
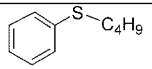
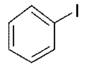
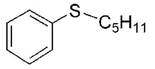
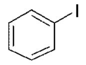
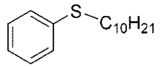
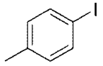
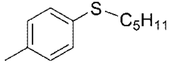
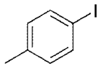
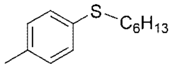
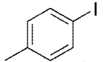
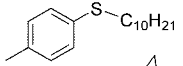
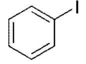
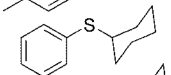
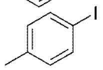
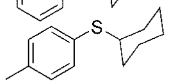
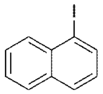
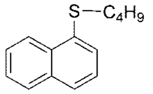
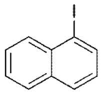
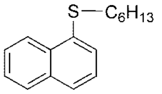
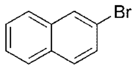
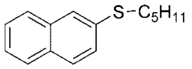
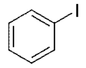
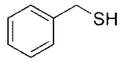
parameters were optimized to develop the scope of this reaction further. First we tried the significant dependence of the S-arylation on the nature of the base and solvents (Table 1). The solvents DMF and toluene were less effective than DMSO. A variety of bases were screened in which Cs_2CO_3 and KOH provided the arylated compound in moderate to excellent yields (Table 1, entries 2, 4). Other bases such as K_3PO_4, KO^tBu, and NaOMe gave trace amounts of diaryl sulfide (Table 1, entries 1, 3, 7).

Table 5. C−S Cross-Coupling of Aryl Halides with Aromatic Thiols[a]

entry	aryl iodide	thiol	product		yield[b] (%)
1	 X = Cl			**1a**	5
2	Br				51
3	I				97
4				**1b**	85
5				**1c**	80
6				**1d**	91
7				**1e**	93
8				**1f**	94
9				**1g**	10
10				**1h**	88
11				**1i**	89
12				**1j**	91
13				**1k**	86
14				**1l**	55
15			-		-

[a] Reaction conditions: aryl halides (1.1 mmol), benzenethiols (1.0 mmol), In_2O_3 (3.0 mol %), KOH (2.0 equiv), DMSO (2.0 mL), 135 °C, 24 h, under a nitrogen atmosphere. [b] Isolated yield.

Table 6. C−S Cross-Coupling of Aryl Halides with Alkyl Thiols[a]

entry	aryl iodide	thiol	product		yield[b] (%)
1		C_4H_9SH		**2a**	91
2		$C_5H_{11}SH$		**2b**	89
3		$C_{10}H_{21}SH$		**2c**	81
4		$C_5H_{11}SH$		**2d**	84
5		$C_6H_{13}SH$		**2e**	81
6		$C_{10}H_{21}SH$		**2f**	79
7				**2g**	91
8				**2h**	87
9		C_4H_9SH		**2i**	89
10		$C_6H_{13}SH$		**2j**	86
11		$C_5H_{11}SH$		**2k**	60
12			-		-

[a] Reaction conditions: Iodobenzene (1.1 mmol), alkyl thiols (1.0 mmol), In_2O_3 (3.0 mol %), KOH (2.0 equiv), DMSO (2.0 mL), 135 °C, 24 h, under a nitrogen atmosphere [b] Isolated yield.

The influence of the amount of In_2O_3 catalyst was also evaluated. As shown in Table 2, The amount of catalyst loading had an impact on the yield. The yield was highly dependent upon the reaction temperature, base, solvent and catalyst. The optimum reaction conditions for the desired C−S cross-coupling were found to be 3.0 mol % of In_2O_3, 2.0 equiv of KOH, 135 °C temperature with DMSO (2.0 mL) as the solvent to obtain 97% of the diphenyl sulfide (Table 1, entry 4).

We have also made a study of C−S cross-coupling with various sulfur nucleophiles under these conditions (Table 3). It is surprising to observe the cleavage of S−S and S−N bonds of diphenyl disulfide and *N*-(phenylthio) phthalimide to provide the corresponding cross-coupling products in 60% and 88% yields respectively. Among these reagents benzenethiol is inexpensive, and therefore we preferred benzenethiols for the C−S cross-coupling reaction.

Next, we studied the effect of various metal nanoparticles on the aryl sulfide formation with KOH in DMSO at 135 °C (Table 4). Among these metal nanoparticle In_2O_3 was found to be a very effective catalyst for C−S coupling reaction. The coupling reaction did not occur in the absence of the catalyst (Table 4, entry 6).

Furthermore, iodobenzene was found to be a more reactive substrate than chloro and bromobenzenes (Table 5, entries 1, 2, 3).

To explore the scope of the reaction, various aryl halides were reacted with different substituted aromatic thiols (Table 5, entries 1−15). In general, all reactions were very clean and the diaryl sulfide derivatives were obtained in high yields under the optimized conditions. It is observed that the electron donating substituents in thiols increased the yields of the products (Table 5, entries 6, 7 and 8). Utilizing these conditions, various alkyl thiols were reacted with different substituted aryl halides (Table 6, entries 1−12). It is observed that an increase in the size of the alkyl chain led to a slight decrease in the yield of the aryl sulfides. However the coupling of heterocyclic thiol (Table 5, entry 15) and benzyl thiol (Table 6, entry 12) with aryl iodide was not successful. These reactions resulted in the formation of only disulfides with the recovery of the starting iodobenzene.

To check the recyclability of the catalyst, it was separated from the reaction mixture by ultra centrifugation, washed with water, dried under vacuum and reused for further catalytic reactions. The catalyst maintained its high level of activity even after being recycled four times as shown in Table 7.

Table 7. Recycling of In_20_3 Nanoparticles

recycles	yield (%)	catalyst recovery (%)
1	97	95
2	95	92
3	92	90
4	92	90

In conclusion, In_2O_3 as nanoparticle has been shown to be an active, stable, inexpensive and nontoxic catalyst for carbon−sulfur bond formation of both aromatic and aliphatic thiols under ligand free conditions in excellent yields. This method precludes the use of ligands and provides in most cases the desired sulfide in high yields. The catalyst can be easily recovered and reused. We are in the process of expanding the substrate scope of these reactions.

Acknowledgment. V.P.R. thanks CSIR, and A.V.K. and K.S. thank UGC, New Delhi, for the award of fellowships.

Supporting Information Available: Detailed experimental procedures and copies of analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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