DOI: 10.1002/ejoc.200900989

Lanthanum(III) Oxide as a Recyclable Catalyst for the Synthesis of Diaryl Sulfides and Diaryl Selenides

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Keywords: Cross-coupling / Selenium / Sulfur / Lanthanum / Sustainable chemistry

La_2O_3 as a new and efficient recyclable catalyst in coupling various aryl halides with aromatic/alkyl thiols and diphenyl diselenide in combination with KOH as a base and DMEDA as a ligand in DMSO at 110 °C is reported.

Introduction

Diaryl sulfide and diaryl selenide functionalities are found in numerous drugs with a broad spectrum of therapeutic activities such as antidiabetes, anti-inflammatory, anti-Alzheimer's, anti-Parkinson's,[1] anticancer,[2] and anti-HIV.[3] C–S and C–Se coupling processes are much less studied when compared to C–N and C–O processes. Mercaptans and benzeneselenols have an inherent property to undergo oxidative S–S and Se–Se bond formation, leading to the formation of disulfides and diselenides, which are unwanted side products. Organic sulfur compounds have a tendency to bind to metals, acting as metal deactivators.[4] The traditional methods for C–S and C–Se cross-coupling reactions often require high reaction temperatures (>200 °C), toxic polar solvents such as quinoline, HMPA, and *N*,*N*-dimethylacetamide, as well as strong reducing agents such as DIBAL-H or $LiAlH_4$.[5] Several transition metals such as palladium,[6] nickel,[7] and cobalt[8] and copper salts[9] in combination with various ligands are generally employed in bringing out this coupling process.[10]

Notable amongst palladium catalysis for C–S cross-coupling reactions are the synthesis of substituted benzothiazoles from 2-bromoanilides[11] and the synthesis of oligothioethers from aryl iodides and aromatic thiols.[12] Recently, Hartwig et al. explored Josiphos CyPF-*t*Bu as a ligand in combination with $Pd(OAc)_2$ to activate aryl chlorides to cross couple with thiols in the presence of low catalyst loadings.[13] Perrio et al. reported a $Pd_2(dba)_3$/Xantphos catalytic system to cross couple aliphatic and aromatic thiols with aryl bromides/triflates in xylene at 140 °C.[14] Nickel also has equally played an important role in the cross-coupling of various aryl halides with thiols. Mozumdar et al. reported a novel method with the use of Ni nanoparticles as an efficient catalytic system with high turnover numbers (TONs) for the selective oxidative coupling of thiols with alcohols to form the corresponding thioethers.[15] Ying et al. reported for the first time nickel N-heterocyclic carbene (Ni-NHC) catalysts with excellent activities.[16] and Takeda et al. reported the conversion of (*E*)-alkenyl halides into (*E*)-alkenyl sulfides by nickel(0) triethyl phosphate.[17]

Generally, copper salts are required in greater than stoichiometric amounts. From an industrial perspective, copper salts are attractive for C–S and C–Se coupling reactions. Traditional copper catalytic systems have lacked efficacy and widespread applicability towards polyfunctionalized substrates.[18,19] Palomo and co-workers reported C–S cross-coupling by employing 20 mol-% CuBr and extremely expensive phosphazene bases.[20] Venkataraman[21] reported an elegant protocol utilizing 10 mol-% CuI in the presence of NaO*t*Bu. In the recent past, several transition metal recyclable catalytic systems such as CuO[22] and In_2O_3 nanoparticles[23] and $NiCl_2{\cdot}H_2O$/TBAB[24] were designed to afford cross-coupled products. Very recently, Wang et al. reported CuI/PEG as a recyclable catalytic system.[25] Although wider reaction conditions existed in the literature for C–S and C–Se coupling processes,[26] in view of several limitations, exploring new catalytic systems, which are inexpensive, air resistant, and recyclable, to afford diaryl thioether and diarylselenide linkages is always desirable. Herein we wish to report inexpensive and moisture-stable lanthanum oxide catalyzed synthesis of diaryl thioether and diaryl selenide derivatives. To the best of our knowledge, this is the first report on lanthanum oxide catalyzed coupling of aryl iodides with thiols or diphenyl diselenide to form aryl sulfides and selenides.

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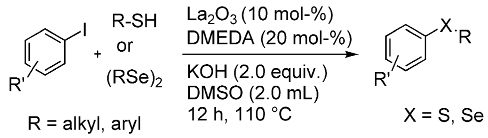
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900989.

Results and Discussion

In our initial study towards the development of La_2O_3-catalyzed C–S cross-coupling reactions, we chose iodobenzene (1.1 mmol) and thiophenol (1.0 mmol) as model substrates with the use of KOH as base in DMSO (Scheme 1). In the absence of ligand, La_2O_3 gave diphenyl sulfide in 42% yield in 24 h, which encouraged us to explore the optimized reaction conditions to increase the yield.



Scheme 1. Synthesis of diaryl sulfides and diaryl selenides.

A wide range of bases including K_2CO_3, Cs_2CO_3, KOH, K_3PO_4, and KO*t*Bu were screened for their efficacy. KOH gave an excellent yield of the cross-coupled product (Table 1, Entry 3) among these bases. The solvent had a significant effect on the product yield. Solvents such as toluene, DMF, and 1,4-dioxane were less effective when compared to DMSO (Table 2, Entry 3). However, in the absence of La_2O_3 with KOH as base no reaction took place at 110 °C even after 36 h.

Table 1. Screening of bases for La_2O_3-catalyzed C–S coupling.[a]

Entry	Base	Yield [%][b]
1	K_2CO_3	66
2	Cs_2CO_3	84
3	KOH	91
4	KO*t*Bu	79
5	K_3PO_4	81

[a] Reaction conditions: iodobenzene (1.1 mmol), benzenethiol (1.0 mmol), La_2O_3 (10 mol-%), *N*,*N*′-dimethylethylenediamine (DMEDA; 20 mol-%), base (2.0 equiv.), DMSO (2.0 mL), 110 °C, 12 h, under a nitrogen atmosphere. [b] Isolated yield.

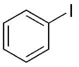
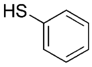
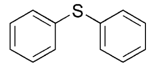
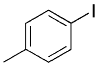
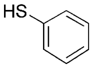
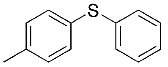
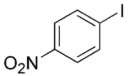
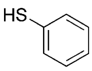
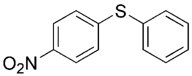
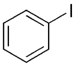
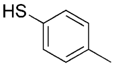
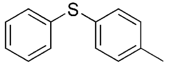
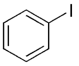
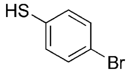
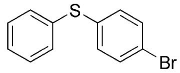
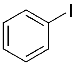
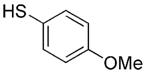
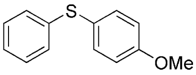
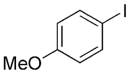
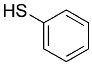
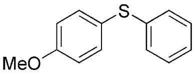
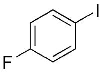
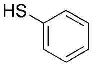
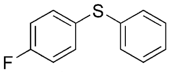
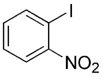
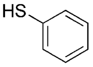
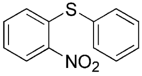
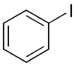
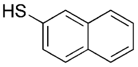
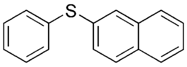
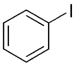
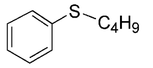
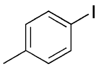
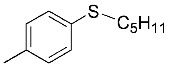
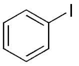
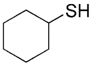
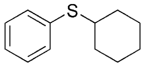
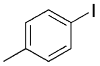
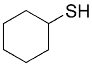
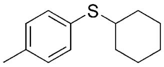
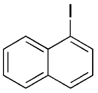
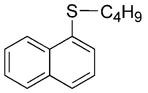
Table 2. Screening of solvents for La_2O_3-catalyzed C–S coupling.[a]

Entry	Solvent	Yield [%][b]
1	toluene	66
2	DMF	84
3	DMSO	91
4	1,4-dioxane	79

[a] Reaction conditions: iodobenzene (1.1 mmol), benzenethiol (1.0 mmol), La_2O_3 (10 mol-%), DMEDA (20 mol-%), KOH (2.0 equiv.), solvent (2.0 mL), 110 °C, 12 h, under a nitrogen atmosphere. [b] Isolated yield.

To evaluate the scope of the proposed catalytic system, the reaction process was studied with commercially available aryl halides with thiophenols and diphenyl diselenide (Tables 3 and 4). This novel protocol was very efficient to couple electron-rich and electron-poor iodobenzene with different thiophenols as well as diphenyl diselenide. In this coupling process we observed that the substituents on aryl iodides and thiols played a substantial role in governing the product yield.

Table 3. Cross-coupling of aryl halides with aromatic and aliphatic thiols.[a]

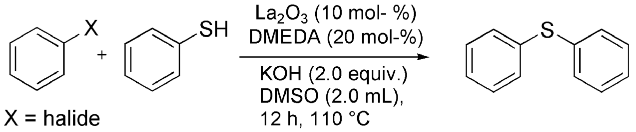
Entry	Aryl iodide	Thiol	Product	Yield[b] [%]
1			 **3a**	91
2			 **3b**	80
3			 **3c**	85
4			 **3d**	90
5			 **3e**	89
6			 **3f**	88
7			 **3g**	81
8			 **3h**	85
9			 **3i**	60
10			 **3j**	88
11		C_4H_9SH	 **3k**	89
12		$C_5H_{11}SH$	 **3l**	84
13			 **3m**	85
14			 **3n**	82
15		C_4H_9SH	 **3o**	80

[a] Reaction conditions: aryl halide (1.1 mmol), benzenethiol (1.0 mmol), La_2O_3 (10 mol-%), DMEDA (20 mol-%), KOH (2.0 equiv.), DMSO (2.0 mL), 110 °C, 12 h, under a nitrogen atmosphere. [b] Isolated yield.

Electron-donating groups on the aryl iodide decreased the product yield (Table 3, Entry 7), whereas the same substituent on the thiol part gave good yield (Table 3, Entry 6). In the case of aliphatic thiols, as the carbon chain length was increased a slight decrease in the product yield was observed (Table 3, Entry 12). Moreover, sterically *ortho*-substituted iodobenzenes did not hamper the reaction (Table 3, Entry 9).

To check the reactivity of different halide groups on the benzene ring towards this reaction, we treated bromobenzene and chlorobenzene with benzenethiol under the same reaction conditions. It was observed that the thioetherification reaction with benzenethiol was more fruitful in the case of iodobenzene than with bromobenzene, resulting in the cross-coupled product in 91 and 67%, respectively (Table 4). The reaction with chlorobenzene was not successful. Hence, the order of reactivity for the thioetherification of aryl halides with benzenethiol catalyzed by La_2O_3 and DMEDA as ligand is ArI > ArBr > ArCl (no reaction).

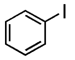
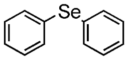
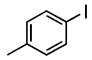
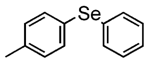
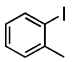
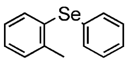
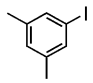
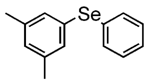
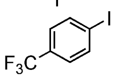
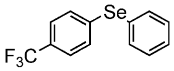
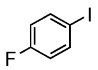
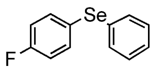
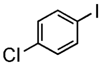
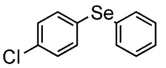
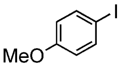
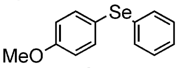
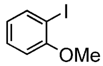
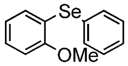
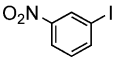
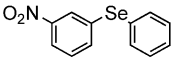
Table 4. Comparison of coupling reactivity of different aryl halides with benzenethiol.[a]



Halide [X]	Yield [%] [b]
X = I	91
X = Br	67
X = Cl	n.r.[c]

[a] Reaction conditions: aryl halide (1.1 mmol), benzenethiol (1.0 mmol), La_2O_3 (10 mol-%), DMEDA (20 mol-%), KOH (2.0 equiv.), DMSO (2.0 mL), 110 °C, 12 h, under a nitrogen atmosphere. [b] Isolated yield. [c] n.r. = no reaction.

Table 5. Cross-coupling of aryl halides with diphenyl diselenide.[a]

Entry	Aryl iodide	Product		Yield[b] [%]
1			**4a**	90
2			**4b**	88
3			**4c**	85
4			**4d**	86
5			**4f**	81
6			**4g**	84
7			**4h**	87
8			**4i**	83
9			**4j**	78
10			**4k**	61

[a] Reaction conditions: aryl halide (1.1 mmol), diphenyl diselenide (0.5 mmol), La_2O_3 (10 mol-%), DMEDA (20 mol-%), KOH (2.0 equiv.), DMSO (2.0 mL), 110 °C, 12 h, under a nitrogen atmosphere. [b] Isolated yield.

The optimized catalytic system was applied for the C–Se bond-formation reaction by treating various iodobenzenes with diphenyl diselenide. This novel protocol gave diaryl selenides in moderate to good yields (Table 5).

The catalyst was found to be recyclable without loss of its catalytic activity up to four cycles. After the reaction of iodobenzene with thiol, the catalyst was recovered by centrifugation. The catalyst was dried under vacuum and reused as shown in (Table 6).

Table 6. Recycling of La_2O_3.[a]

Cycle	Catalyst recovery [%]	Yield [%][b]
1	97	91
2	95	85
3	92	81
4	89	76

[a] Iodobenzene (1.1 mmol), benzenethiol (1.0 mmol), La_2O_3 (10 mol-%), DMEDA (20 mol-%), KOH (2.0 equiv.), DMSO (2.0 mL). [b] Isolated yield.

Conclusions

In summary, we have demonstrated an efficient protocol for the synthesis of diphenyl sulfides and selenides by using lanthanum oxide as a recyclable catalytic system.

Experimental Section

General Procedure for the La_2O_3-Catalyzed Formation of Diphenyl Sulfide (3a): To a stirred solution of iodobenzene (1.1 mmol) and benzenethiol (1.0 mmol) in dry DMSO (2.0 mL) was added La_2O_3 (10 mol-%) and DMEDA (20 mol-%), followed by KOH (2.0 equiv.), and the mixture was heated at 110 °C under a nitrogen atmosphere for 12 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extract was dried with anhydrous Na_2SO_4. The solvent was completely removed under vacuum to give the crude product, which was purified by column chromatography (petroleum ether/ethyl acetate, 99:1) to yield expected product **3a** (169 mg, 91% yield as colorless oil). The identity and purity of the product was confirmed by ^1H and ^{13}C NMR spectroscopic analysis.

General Procedure for the La_2O_3-Catalyzed Formation of Diphenyl Selenide (4a): To a stirred solution of iodobenzene (1.1 mmol) and diphenyl diselenide (0.5 mmol) in dry DMSO (2.0 mL) was added La_2O_3 (10 mol-%) and DMEDA (20 mol-%), followed by KOH (2.0 equiv.), and the mixture was heated at 110 °C under nitrogen atmosphere for 12 h. The progress of the reaction was monitored by TLC. After the reaction was complete, the reaction mixture was extracted with ethyl acetate (3 × 10 mL). The combined organic extract was dried with anhydrous Na_2SO_4. The solvent was completely removed under vacuum to give the crude product, which was purified by column chromatography.

Recycling Experiment for Catalyst Recovery: After completion of the reaction, ethyl acetate and water were added to the reaction mixture, which was stirred for 15 min and then centrifuged. The recovered catalyst was washed with ethyl acetate followed by acetone and dried under vacuum. The recovered catalyst was used up to four cycles.

Supporting Information (see footnote on the first page of this article): Experimental procedures; characterization of the C–S and C–Se cross-coupled products, including ^{1}H & ^{13}C NMR spectra.

Acknowledgments

S. N. M., B. M. and V. P. R. are grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi, India for providing fellowships.

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Received: August 31, 2009