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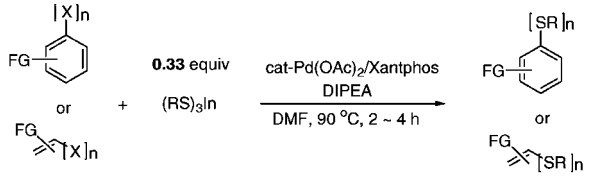
Palladium-Catalyzed Carbon−Sulfur Cross-Coupling Reactions with Indium Tri(organothiolate) and Its Application to Sequential One-Pot Processes

Jae-Young Lee and Phil Ho Lee*

National Research Laboratory for Catalytic Organic Reaction, Department of Chemistry, and Institute for Molecular Science and Fusion Technology, Kangwon National University, Chuncheon 200-701, Republic of Korea

phlee@kangwon.ac.kr

Received June 17, 2008



It was found that indium tri(organothiolate) is an effective nucleophilic coupling partner in Pd-catalyzed C−S cross-coupling reactions to produce the functionalized sulfides in excellent yields with high atom efficiency and complete regio- and chemoselectivity. The present method was efficiently applied to the sequential one-pot processes composed of selective double C−S cross-coupling reactions and addition of allylindium or allenylindium to aldedyde to give the functionalized sulfides and bis(sulfides).

The sulfide group is a key motif in chemistry and biology. Because of the characteristic features of the C−S bond as a function of biological, pharmaceutical, and material sciences,[1] transition metal, such as Pd,[2] Ni,[3] Cu,[4] Co,[5] Rh,[6] Pt,[7] and Fe,[8] catalyzed C−S cross-coupling reactions have received much attention and been studied by means of the development of new catalytic systems and appropriate reagents. Especially, the synthesis of sulfides catalyzed by palladium has shaped up by employment of the newly designed phosphine ligand, which creates a long-lived catalyst.[2a,c] Although interesting C−S cross-coupling reactions have been reported, they usually required harsh conditions such as excess use of thiol, high reaction temperature (100−150 °C), and long reaction time (∼24 h). Especially, C−S cross-coupling reactions with volatile thiols, such as *n*-propyl thiol and isopropyl thiol, were difficult. Therefore, the development of efficient catalytic systems to overcome these difficulties is still needed. Recently, we reported novel and efficient Pd-catalyzed C−C cross-coupling reactions using allylindiums, allenylindiums, tri(organo)indiums, and tetra(organo)indates on the basis of the intriguing chemical properties of indium metal.[9] However, C−S cross-coupling reactions with organoindium reagents have not been reported despite one of the principal methods of forming C-heteroatom bonds. These results have led us to investigate the participation of organoindium reagents in C−S cross-coupling reactions. In continuation of our studies directed toward the development of efficient indium-mediated reactions, we described herein indium tri(organothiolate), derived from a variety of volatile as well as nonvolatile thiols, as the nucleophilic cross-coupling partners in Pd-catalyzed C−S cross-coupling reactions. Also, their applications to sequential one-pot processes in combination with allyl- and allenylindiums led to the formation of functionalized sulfides and bis(sulfides).

First, the catalytic activity of several palladium complexes was examined in the reaction of 2-bromonaphthalene (**2a**) with indium tri(benzenethiolate) (**1a**),[10] which was produced from the reaction of indium with phenyl disulfide. The results are summarized in Table 1. Among the catalysts examined, 4 mol

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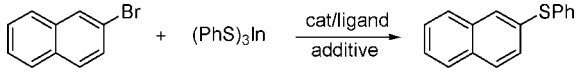
10.1021/jo801169h CCC: $40.75 © 2008 American Chemical Society
Published on Web 08/20/2008

TABLE 1. Reaction Optimization for C−S Cross-Coupling Reactions[a]



2a 1a 3a

entry	catalyst	ligand	additive	solvent	yield (%)[b]
1				DMF	0
2			DIPEA[c]	DMF	0
3	$Pd(OAc)_2$	Ph_3P	DIPEA	DMF	trace
4	$Pd(OAc)_2$	(Biph)PCy_2[d]	DIPEA	DMF	68(26)[e,f]
5	$Pd(OAc)_2$	DPEphos	DIPEA	DMF	94
6	$Pd(OAc)_2$	Xantphos	DIPEA	DMF	99(95)[f]
7	$Pd_2dba_3CHCl_3$	Xantphos	LiCl	DMF	91[g]
8	$Pd_2dba_3CHCl_3$	Xantphos	DIPEA	DMF	95[g]
9	$Pd(OAc)_2$	Xantphos		DMF	70
10	$Pd(OAc)_2$	Xantphos	DIPEA	THF	30
11	$Pd(OAc)_2$	Xantphos	DIPEA	Xylene	75
12	$Pd(OAc)_2$	Xantphos	DIPEA	DMF	30[h]
13	$Pd(OAc)_2$	Xantphos	DIPEA	DMF	0[i]
14	$Pd(OAc)_2$	Xantphos	DIPEA	DMF	0[j]
15	$Pd(OAc)_2$	Xantphos	DIPEA	DMF	10[k]

[a] Reactions were performed with **2a** (1.0 equiv), **1a** (0.34 equiv), and additive (1 equiv) in the presence of 4 mol % of $Pd(OAc)_2$ and 4.2 mol % of ligand at 100 °C for 4 h in DMF (0.2 M) unless otherwise noted. [b] GC yields with $C_{14}H_{30}$ as an internal standard. [c] Diisopropylethylamine. [d] 8 mol % of ligand was used. [e] Yield of 1,1′-binaphthyl. [f] Isolated yield. [g] 2 mol % of $Pd_2dba_3CHCl_3$ and 4 mol % of Xantphos was used. [h] PhSH (1.2 equiv) was used instead of $(PhS)_3In$. [i] PhSSPh (1.2 equiv) was used instead of $(PhS)_3In$. [j] PhSLi was used instead of $(PhS)_3In$. [k] PhSLi/$InCl_3$ was used instead of $(PhS)_3In$.

% of $Pd(OAc)_2$ showed high catalytic activity. Other palladium complexes, such as $Pd_2dba_3CHCl_3$ and $(Ph_3P)_4Pd$, produced 2-naphthyl phenyl sulfide (**3a**) in good yields. Among the ligands examined, Xantphos gave the best results (entry 6). The use of DIPEA (*i*-Pr_2NEt) and LiCl as additive increased the yield (entries 6 and 7 vs. 9).[11] Of the catalytic systems examined, the best results were obtained with 4 mol % of $Pd(OAc)_2$ and 4.2 mol % of Xantphos in the presence of DIPEA (1 equiv) in DMF (100 °C, 4 h)[12] under a nitrogen atmosphere, affording **3a** in 95% yield (entry 6). This result indicated that three phenylthio groups in **1a** were transferred to **2a** with high atom efficiency. Except for DPEphos, the other choices of ligands such as Ph_3P and (Biph)PCy_2 were not effective under these conditions (entries 3−5). Solvents other than DMF afforded low yield (entries 10 and 11). Reaction of **2a** with **1a** without Pd catalyst did not produce **3a**, indicating that the present reactions proceeded through the cross-coupling reaction (entry 1). Although thiophenol and phenyl disulfide were employed as nucleophilic coupling partners, less pleasant results were obtained (entry 12 and 13). In addition, the possibility of a ligand dissociation of $(PhS)_3In$ was examined under the reaction conditions. 2-Bromonaphthalene did not react with lithium benzenthiolate under the optimum reaction conditions (entry 14). These results indicated that ligand dissociation of $(RS)_3In$ did not occur during the cross-coupling reactions and **3a** was obtained through the cross-coupling reaction.

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to various functionalized aryl and vinyl halides and triflates with indium tri(organothiolate) containing aryl and alkyl thiolates (Table 2). Reaction of **1a** with 1-iodonaphthalene and 1-naphthyl triflate gave 1-naphthyl phenyl sulfide in 95% yields (entries 1 and 2). However, 1-chloronaphthalene did not react with **1a** (entry 3). Under the optimized conditions, **2a** was treated with a variety of indium tri(organothiolates) (**1b**, **1c**, **1d**, and **1e**), such as indium tri(4-fluoro-, 4-methyl-, and 4-methoxybenzenethiolate) and indium tri(*tert*-butylthiolate), to produce the desired sulfides in good to excellent yields (entries 5−8). These results suggested that the three organothio groups in indium tri(organothiolate) were moved to **2a** with high atom efficiency. The presence of various substituents, e.g., formyl (entry 9), acetyl (entry 10), nitrile (entry 12), nitro (entry 13), ethoxycarbonyl (entries 15−17), methoxy (entry 19), and dimethylamino (entry 20), on aromatic rings did not show a significant effect on the efficiency of the reactions. Noteworthy is the fact that protection of an aldehyde and ketone group on substrates is not necessary, as demonstrated by the reaction of 2-bromobenzaldehyde and 4-bromoacetophenone, respectively (entries 9 and 10). Subjecting aryl triflate to **1a** afforded the desired sulfides in excellent yields (entries 11, 14, and 18). In the case of ethyl bromobenzoate, both the yield and the reaction time are almost independent of the electronic and steric effect (entries 15−17). Especially, C−S cross-coupling reactions with volatile as well as nonvolatile thiols, such as *n*- propyl thiol and isopropyl thiol, clearly proceeded to afford the desired products (entries 16 and 22). 3-Bromoquinoline turned out to be compatible with the reaction conditions (entries 21 and 22).

TABLE 2. Palladium-Catalyzed Cross-Coupling Reactions of $(RS)_3In$ with Aryl Halides and Triflates[a]

$$R^1{-}X + (RS)_3In \rightarrow R^1{-}S{-}R$$

entry	X	R^1	R	yield (%)
1	I	1-Naph	Ph (**1a**)	95 (**3b**)
2	OTf	1-Naph	**1a**	95 (**3b**)
3	Cl	1-Naph	**1a**	0
4	Br	2-Naph	**1a**	95 (**3a**)
5	Br	2-Naph	4-F-C_6H_4 (**1b**)	91 (**3c**)
6	Br	2-Naph	4-Me-C_6H_4 (**1c**)	82 (**3d**)
7	Br	2-Naph	4-MeO-C_6H_4 (**1d**)	90 (**3e**)
8	Br	2-Naph	*t*-Bu (**1e**)	97 (**3f**)
9	Br	2-OHC-C_6H_4	**1a**	95 (**3g**)
10	Br	4-Ac-C_6H_4	**1a**	91 (**3h**)
11	OTf	4-Ac-C_6H_4	**1a**	88 (**3h**)
12	Br	4-NC-C_6H_4	**1a**	82 (**3i**)
13	Br	4-NO_2-C_6H_4	**1a**	90 (**3j**)
14	OTf	4-NO_2-C_6H_4	**1a**	89 (**3j**)
15	Br	2-EtO_2C-C_6H_4	**1a**	91 (**3k**)
16	Br	3-EtO_2C-C_6H_4	*i*-Pr (**1f**)	82 (**3l**)
17	Br	4-EtO_2C-C_6H_4	**1a**	90 (**3m**)
18	OTf	4-EtO_2C-C_6H_4	**1a**	97 (**3m**)
19	Br	4-MeO-C_6H_4	**1a**	97 (**3n**)
20	Br	3-Me_2N-C_6H_4	**1a**	82 (**3o**)
21	Br	3-quinolinyl	**1a**	87 (**3p**)
22	Br	3-quinolinyl	*n*-Pr (**1g**)	85 (**3q**)

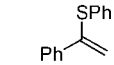
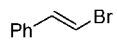
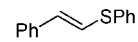
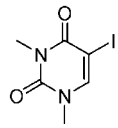
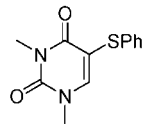
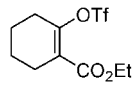
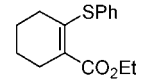
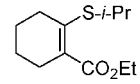
[a] Reactions were performed with 4 mol % of $Pd(OAc)_2$, 4.2 mol % of Xantphos, and $(RS)_3In$ (0.34 equiv) in DMF at 100 °C for 4 h unless otherwise noted.

Next, we applied this catalytic system in a variety of vinyl bromides and triflates. The results are summarized in Table 3. Treatment of α- and β-bromostyrene with $(PhS)_3In$ gave rise to the corresponding sulfides in excellent yields (entries 1 and

(11) Among the additives examined, DIPEA gave the best result. Although reaction of 1-bromonaphthalene with $(PhS)_3In$ produced 1-naphthyl phenyl sulfide in 5% yield, use of DIPEA as an additive afforded the sulfide in 57% yield.

(12) Reaction was almost completed over 95% in GC within 2 h.

TABLE 3. Palladium-Catalyzed Cross-Coupling Reactions of $(RS)_3In$ with Vinyl Halides and Triflates[a]

entry	reactant	product	yield (%)
1			97 (**3r**)
2			95 (**3s**)
3[b]			92 (**3t**)
4			95 (**3u**)
5			93 (**3v**)

[a] Reactions were performed with 4 mol % of $Pd(OAc)_2$, 4.2 mol % of Xantphos, and $(RS)_3In$ (0.34 equiv) in DMF at 100 °C for 4 h, unless otherwise noted. [b] Reaction was carried out with 2 mol % of $Pd(OAc)_2$ and 2.1 mol % of Xantphos in DMF at 90 °C.

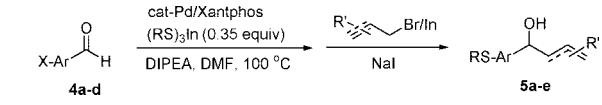
2). Treatment of vinyl iodide possessing the 1,3-dimethyluracil moiety with **1a** gave sulfide **3t** in 92% yield with 2 mol % of $Pd(OAc)_2$ and 2.1 mol % of Xantphos at 90 °C (entries 3). We were pleased to observe that treatment of vinyl triflates with $(RS)_3In$ gave the vinyl sulfides in excellent yields (entries 4 and 5).

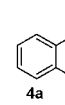
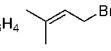
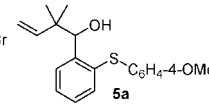
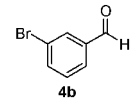
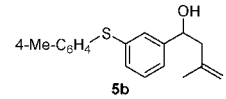
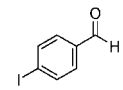
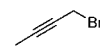
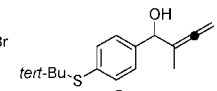
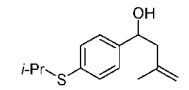
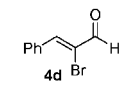
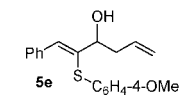
As an extension of this work, we examined the selective C−S cross-coupling reactions and sequential indium-mediated allylation or allenylation reactions in one pot (Table 4). By using halobenzaldehyde (**4a**−**c**) and bromo-α,β-enal (**4d**), aryl-aryl, aryl-alkyl, and aryl-vinyl sulfides possessing homoallyl alcohols **5a**,**b** and **5d**,**e** were produced in good to excellent yields (entries 1−2 and 4−5). Reaction of 2-iodobenzaldehyde with prenylindium generated in situ from prenyl bromide and indium in the presence of NaI was carried out in THF at room temperature, producing addition product. However, when this mixture was treated with $(4\text{-}CH_3\text{-}C_6H_4S)_3In$ in the presence of 2 mol % of $Pd(OAc)_2$ and 2.1 mol % of Xantphos, the desired product was not obtained. *tert*-Butyl aryl sulfide **5c** bearing allenol was selectively obtained in 74% yield in one pot through the C−S cross-coupling reaction and sequential addition of allenylindium obtained from 1-bromo-2-butyne and indium to aldehyde (entry 3).

Encouraged by these results, the present method was applied to the sequential one-pot processes composed of selective double C−S cross-coupling reactions and addition of allylindium to aldehyde. The functionalized bis(sulfides) **6a**, **6b**, and **6c** were selectively produced in good yields with use of the triflate of 2-hydroxy-5-iodobenzaldehyde (Scheme 1). These results indicate that $(RS)_3In$ is inert to aldehyde and aryl iodide is more reactive than aryl triflate in the Pd-catalyzed C−S cross-coupling reaction with $(RS)_3In$.

In summary, we have demonstrated that indium tri(organothiolates) are effective nucleophilic coupling partners in Pd-catalyzed C−S cross-coupling reactions with a variety of electrophiles, producing the functionalized aryl-aryl, aryl-alkyl, aryl-vinyl, and alkyl-vinyl sulfides in excellent yields with high atom efficiency and complete regio- and chemoselectivity.

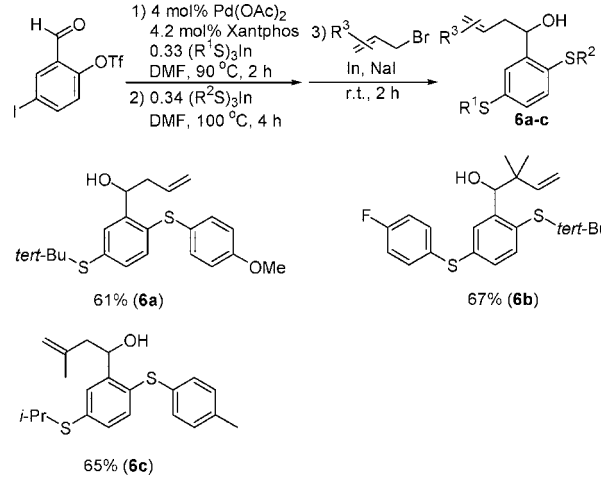
TABLE 4. Sequential One-Pot C−S Cross-Coupling Reactions and Indium-Mediated Addition Reactions[a]



entry	reactant	R	R'–Br	product	yield (%)
1	 **4a**	4-MeO-C_6H_4		 **5a**	86
2	 **4b**	4-Me-C_6H_4		 **5b**	91[b]
3	 **4c**	*tert*-Bu		 **5c**	74
4	**4c**	*i*-Pr		 **5d**	94
5	 **4d**	4-MeO-C_6H_4		 **5e**	90

[a] Cross-coupling reactions were carried out with 2 mol % $Pd(OAc)_2$, 2.1 mol % of Xantphos, and $(RS)_3In$ (0.34 equiv) in DMF for 2 h at 100 °C and addition reactions were carried out with In (1 equiv), the corresponding bromide (1.6 equiv), and NaI (1.6 equiv) at room temperature for 2 h unless otherwise noted. [b] Reactions were carried out with 4 mol % of $Pd(OAc)_2$ and 4.2 mol % of Xantphos for 4 h.

SCHEME 1. Sequential One-Pot Processes with Organoindium Reagents



Furthermore, the sequential one-pot processes with $(RS)_3In$ gave the sulfides and bis(sulfides) having considerable complexity. The present method complements the existing synthetic methods due to wide applicability of $(RS)_3In$ obtained from volatile as well as nonvolatile thiols and its high reactivity and selectivity.

Experimental Section

4-Fluorophenyl 2-Naphthyl Sulfide (3c). To a suspension of $Pd(OAc)_2$ (4.5 mg, 0.020 mmol, 4.0 mol %) and Xantphos (12.1

mg, 0.021 mmol, 4.2 mol %) in DMF (1.0 mL) was added 2-bromonaphthalene (103.5 mg, 0.50 mmol) in DMF (0.5 mL) at room temperature under a nitrogen atmosphere. After being stirred for 5 min, (4-F-$C_6H_4S)_3$In (83.0 mg, 0.167 mmol) and DIPEA (87.0 μL, 0.50 mmol) in DMF (1.0 mL) was transferred via double-ended needle and the mixture was stirred at 100 °C for 4 h. The reaction mixture was quenched with sat. $NaHCO_3$ solution (1.0 mL). The aqueous layer was extracted with ether (3 × 20 mL), and the combined organics were washed with water (10 mL) and sat. NaCl solution (10 mL), dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane) to give **3c** as a white crystal (116.0 mg, 91%). Melting point 67.5−68 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.70 (m, 4H), 7.48−7.44 (m, 2H), 7.41 (dd, 2H, J = 5.2, 8.6 Hz), 7.34 (d, J = 8.6 Hz, 1H), 7.04 (t, J = 8.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, J_{C-F} = 246.3 Hz), 134.0 (d, J_{C-F} = 8.4 Hz), 133.8, 133.7, 132.1, 130.3 (d, J_{C-F} = 3.1 Hz), 128.9, 128.7, 127.8, 127.7, 127.3, 126.7, 126.1, 116.5 (d, J_{C-F} = 22 Hz); IR (KBr) 3049, 1884, 1587, 1490, 1397, 1339, 1218, 862, 812 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{11}FS$ M^+ 254.0565, found 254.0567.

1-[2-(4-Methoxyphenylthio)-5-methylthiophenyl]but-3-en-1-ol (6a). To a suspension of $Pd(OAc)_2$ (3.6 mg, 0.016 mmol, 4.0 mol %) and Xantphos (9.7 mg, 0.017 mmol, 4.2 mol %) in DMF (0.5 mL) was added 2-formyl-4-iodophenyl trifluoromethanesulfonate (152.0 mg, 0.40 mmol) in DMF (0.5 mL) at room temperature under a nitrogen atmosphere. After being stirred for 5 min, (t-BuS)$_3$In (51.0 mg, 0.133 mmol) and DIPEA (69.0 μL, 0.40 mmol) in DMF (0.5 mL) was transferred via double-ended needle and the mixture was stirred at 90 °C for 3 h. The reaction mixture was cooled to room temperature, a solution of (4-MeO-$C_6H_4S)_3$In (72.0 mg, 0.135 mmol) and DIPEA (69.0 μL, 0.40 mmol) in DMF (0.5 mL) was added, then the mixture was stirred at 100 °C. After being stirred for 4 h, the reaction mixture was cooled to room temperature and transferred to a solution of organoindium reagent generated in situ from indium (46.0 mg, 0.40 mmol), NaI (96.0 mg, 0.64 mmol), and allyl bromide (56.0 μL, 0.65 mmol) in DMF (0.5 mL). After being stirred for 2 h at room temperature, the reaction mixture was quenched with sat. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with ether (3 × 20 mL), and the combined organic layers were washed with water and brine, dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc:hexane = 1:10) to give **6a** as yellow oil (91.0 mg, 61%). ^{1}H NMR(400 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.38 (d, J = 8.8 Hz, 2H), 7.24 (d, J = 8.2 Hz, 1H), 6.92(d, J = 8.8 Hz, 2H), 6.86(d, J = 8.2 Hz, 1H), 5.94−5.83 (m, 1H), 5.24 (td, J = 8.2, 3.4 Hz, 1H), 5.22−5.16 (m, 2H), 3.83 (s, 3H), 2.66−2.60 (m, 1H), 2.45 (td, J = 8.0, 14.2 Hz, 1H), 2.21 (d, J = 3.4 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 141.9, 136.8, 136.5, 135.5, 134.8, 134.3, 130.4, 128.7, 123.2, 118.7, 115.2, 69.6, 55.4, 46.1, 42.3, 30.9; IR (Neat) 3445, 3074, 2960, 2862, 2538, 2046, 1891, 1639, 1455, 1249, 827 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{26}O_2S_2$ M^+ 374.1374, found 374.1373.

Acknowledgment. Dedicated to Professor Junghun Suh on the occasion of his 60th birthday.This work was supported by the Korea Science and Engineering Foundation (KOSEF) through the National Research Laboratory Program funded by the Ministry of Science and Technology (No. M10600000203-06J0000-20310). The NMR was obtained from the central instrumental facility in Kangwon National University. Dr. Sung Hong Kim at the KBSI (Daegu) is thanked for obtaining the MS data.

Supporting Information Available: Experimental procedure and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801169H