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Palladium-catalyzed Carbon–Sulfur Cross-coupling Reactions of Aryl Chlorides with Indium Tris(organothiolates)

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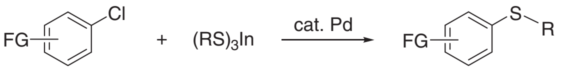
Pd-Catalyzed carbon–sulfur cross-coupling reactions of aryl chlorides with indium tris(organothiolates) were developed. Aryl chlorides reacted with indium tris(organothiolates) (0.35 equiv) in the presence of 4 mol % of Pd(OAc)$_2$, 4.2 mol % of Xantphos, and Cs_2CO_3 as an additive, producing aryl–aryl and aryl–alkyl sulfides in good to excellent yields.

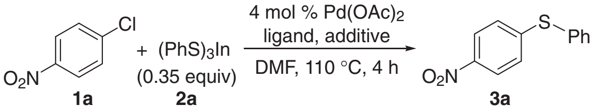
Cross-coupling reaction is one of the most straightforward and versatile methods in organic synthesis.[1] Advances in transition-metal catalysis make it possible to couple an electrophilic coupling partner with a nucleophilic coupling partner with high efficiencies and broad substrate scopes. Especially, the transition-metal-catalyzed carbon–sulfur cross-coupling reaction is one of the fundamental processes in organic synthesis because the sulfide group is widely used in pharmaceuticals, functional materials, and synthesis of natural products.[2] Over the last decades, transition metals, such as Pd,[3] Ni,[4] Cu,[5] and Fe,[6] have been applied in carbon–sulfur cross-coupling reactions, leading to the effective synthesis of sulfides. In continuation of our studies directed toward the development of efficient indium-mediated organic reactions, we reported Pd-catalyzed cross-coupling reactions using allylindiums,[7] allenylindiums,[8] 1,3-butadien-2-ylindiums,[9] tetra(organo)indates,[10] and vinylindiums[11] with a wide range of functional group tolerance.[10a,12] Moreover, we developed recently indium tris(organothiolate) as a nucleophilic cross-coupling partner in Pd-catalyzed C–S cross-coupling reactions using aryl bromide and iodide as an electrophile.[13] There is great interest in developing carbon–sulfur cross-coupling reactions that use aryl chlorides because they are readily available, inexpensive, and environmentally strategic reagents.[3d,14] Herein, Pd-catalyzed carbon–sulfur cross-coupling reactions of aryl chlorides with indium tris(organothiolates) are described (Scheme 1).



Scheme 1. Pd-Catalyzed C–S cross-coupling reactions of aryl chlorides with indium tris(organothiolates).

Although optimum conditions obtained from Pd-catalyzed C–S cross-coupling reaction of aryl bromide with indium tris(phenylthiolate) applied to *p*-chloronitrobenzene (**1a**), 4-nitrophenyl phenyl sulfide (**3a**) was produced in 30% yield.[13] These results led us to investigate intensively Pd-catalyzed C–S cross-coupling reaction of aryl chloride with indium tris(organothiolate). First, several additives and ligands were examined and the results are summarized in Table 1. Use of sodium iodide gave similar results to DIPEA (Entry 2). Lithium iodide afforded **3a** in moderate yield (Entries 3 and 4), whereas lithium bromide (2 equiv) increased to 75% yield (Entry 6). Next, a wide range of ligand in the presence of lithium bromide (2 equiv) as an additive was examined (Entries 7–11). Although Cy_3P, (p-MeO-C_6H_4)$_3$P, and (p-CF_3-C_6H_4)$_3$P did not give **3a**, (Biph)PCy$_2$ and DPEDIPphos produced **3a** in 78% and 81% yields, respectively (Entries 7 and 9). Coupling reaction did not proceed with Na_2CO_3 as an additive (Entry 12). However, use of Cs_2CO_3 (2 equiv) with 4 mol % Pd(OAc)$_2$ and 4.2 mol % Xantphos in DMF (110 °C, 4 h) provided **3a** in 92% yield (Entry 14). It is noteworthy that (PhS)$_3$In (0.35 equiv) gave the best result, indicating that all phenylthiolate groups attached to indium were transferred to **1a** with high atom efficiency.

Table 1. Effect of additive and ligand on C–S cross-coupling reactions

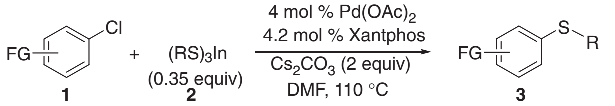


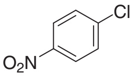
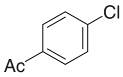
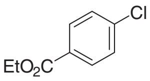
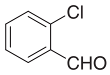
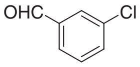
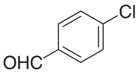
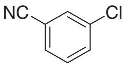
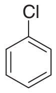
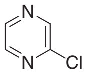
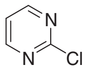
Entry	Additive (equiv)	Ligand[a] (mol %)	Yield[b]/%
1	DIPEA[c] (1)	Xantphos (4.2)	30
2	NaI (1)	Xantphos (4.2)	30
3	LiI (1)	Xantphos (4.2)	52
4	LiI (2)	Xantphos (4.2)	50
5	LiBr (1)	Xantphos (4.2)	69
6	LiBr (2)	Xantphos (4.2)	75
7	LiBr (2)	(Biph)PCy$_2$ (8.2)	78
8	LiBr (2)	Cy_3P (8.2)	0
9	LiBr (2)	DPEDIPphos (4.2)	81
10	LiBr (2)	(p-MeO-C_6H_4)$_3$P (8.2)	0
11	LiBr (2)	(p-CF_3-C_6H_4)$_3$P (8.2)	0
12	Na_2CO_3 (2)	Xantphos (4.2)	0
13	Cs_2CO_3 (1)	Xantphos (4.2)	84
14	Cs_2CO_3 (2)	Xantphos (4.2)	92

[a] Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, (Biph)PCy$_2$: 2-(dicyclohexylphosphino)biphenyl, DPEDIPphos: bis(2-diisopropylphosphinophenyl)ether. [b] Isolated yield. [c] DIPEA: Diisopropylethylamine.

To demonstrate the efficiency and scope of the present method, we applied this catalytic system to various functionalized aryl chlorides **1** with indium tris(organothiolate) **2** containing aryl and alkyl groups and the results are summarized in Table 2. Reaction of **1a** with indium tris(isopropylthiolate) (**2b**) gave isopropyl 4-nitrophenyl sulfide (**3b**) in 71% yield (Entry 1). Although treatment of 4-chloroacetophenone having labile ketone group with indium tris(phenylthiolate) (**2a**)

Table 2. Pd-Catalyzed C–S cross-coupling reactions of aryl chlorides with indium tris(organothiolates)



Entry	Aryl chloride	R	Sulfide	Time/h	Yield[a]/%
1	 **1a**	*iso*-Pr (**2b**)	**3b**	3	71
2	 **1b**	*tert*-Bu (**2c**)	**3c**	2	70
3		Ph (**2a**)	**3d**	3	88
4	 **1c**	**2a**	**3e**	4	53
5		*p*-Anisyl (**2d**)	**3f**	4	52
6		*p*-Tolyl (**2e**)	**3g**	4	55
7	 **1d**	**2c**	**3h**	2	82
8		**2a**	**3i**	4	89
9	 **1e**	**2a**	**3j**	4	19
10	 **1f**	**2c**	**3k**	4	81
11		**2a**	**3l**	4	86
12	 **1g**	**2c**	**3m**	2	42
13		**2a**	**3n**	4	25 (50)[b]
14	 **1h**	**2d**	—	15	0
15	 **1i**	**2c**	**3o**	2	39
16		**2c**	**3o**	2	78[c]
17		**2a**	**3p**	2	97[c]
18	 **1j**	**2c**	**3q**	2	86
19		**2c**	**3q**	2	91[c]
20		**2d**	**3r**	2	65

[a] Isolated yield. [b] Recovery yield of starting material. [c] DIPEA (1 equiv) was used.

provided the corresponding sulfide **3d** in 88% yield, indium tris(*tert*-butylthiolate) (**2c**) gave somewhat lower yield (70%) due to steric hindrance (Entries 2 and 3). However, ethyl 4-chlorobenzoate reacted with a variety of indium tris(arylthiolate) (**2a**, **2d**, and **2e**) afforded sulfides in 52–55% yields using Cs$_2$CO$_3$ (2 equiv) (Entries 4, 5, and 6). Both 2- and 4-chlorobenzaldehyde (**1d** and **1f**) reacted with 0.35 equivalent of **2c** and **2a**, producing the desired sulfides in excellent yields (81–89%), indicating that all of the thiolate groups were transferred from indium to **1d** and **1f** with high atom efficiency (Entries 7, 8, 10, and 11). Unfortunately, 3-chlorobenzaldehyde (**1e**) provided the sulfide in 19% yield (Entry 9). Reaction of 3-chlorobenzonitrile (**1g**) with **2c** gave *tert*-butyl 3-cyanophenyl sulfide (**3m**) in 42% yield (Entry 12). Exposure of 2-chloropyrazine (**1i**) to **2c** with Cs$_2$CO$_3$ produced *tert*-butyl 2-pyrazolyl sulfide (**3o**) in 39% yield (Entry 15). However, use of DIPEA as an additive gave **3o** and **3p** in 78% and 97% yield, respectively, in the reaction of **1i** with **2c** and **2a** (Entries 16 and 17). We believe that DIPEA as a base might trap indium chloride and then, yield of sulfide increase (Entry 15 vs. 16 and Entry 18 vs. 19). We were pleased to obtain *tert*-butyl and 4-methoxyphenyl 2-pyrimidinyl sulfide (**3q** and **3r**) from the treatment of 2-chloropyrimidine (**1j**) with indium tris(organothiolate) **2c** and **2d** under the optimum reaction conditions (Entries 18 and 20). Moreover, subjecting **1j** to **2c** with DIPEA afforded **3q** in 91% yield (Entry 19). The present reaction did not proceed without Pd catalyst, indicating that the reaction occurred through cross-coupling reaction. However, chlorobenzene and aryl halide having electron-donating groups such as methyl and methoxy did not give sulfide under the present conditions (Entry 14).

Although thiols in transition-metal-catalyzed cross-coupling reactions were directly used as a nucleophilic coupling partner, functional group tolerance is not so good sometimes. However, the present reaction proceeded smoothly to provide the desired sulfide in good yield regardless of the presence of labile ethoxycarbonyl and formyl groups. Electrophilic coupling partners have only stable functional groups such as methyl, methoxy, fluoride, amino, nitro, and hydroxy.[15] For control experiment, reaction of chlorobenzaldehyde and ethyl 4-chlorobenzoate with benzenethiol using KOH/DMSO at 130 °C was carried out, providing the corresponding sulfide in low yield.

In summary, we have developed Pd-catalyzed carbon–sulfur cross-coupling reactions of aryl chlorides with indium tris(organothiolates). Aryl chlorides having an electron-withdrawing group such as formyl, acetyl, ethoxycarbonyl, and nitro, and nitrogen heteroaryl chlorides reacted with indium tris(organothiolates) (0.35 equiv) in the presence of 4 mol % of Pd(OAc)$_2$, 4.2 mol % of Xantphos, and Cs$_2$CO$_3$ as an additive, producing aryl–aryl and aryl–alkyl sulfides.[16]

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