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A general rhodium-catalyzed cross-coupling reaction of thiols with aryl iodides

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ABSTRACT

The general procedure for the rhodium-catalyzed cross-coupling of thiols with aryl iodides is described. The catalytic system consists of 5 mol % of [RhCl(cod)]₂ and 10 mol % of PPh₃ as a ligand. A variety of aryl iodides reacted with thiols, giving aryl thioethers in good to excellent yields. It is important to note that the deactivated aryl iodides such as 4-iodoanisole is worked smoothly to provide the corresponding aryl thioethers in excellent yields. Functional groups such as free-amines, chloro, are all tolerated under the employed reaction conditions.

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Aryl thioethers are present in many biologically active molecules.¹ As a consequence, many approaches have been described for the synthesis of these compounds.^{2–11} Among these methods, the transition-metal-catalyzed cross-coupling reaction of thiols with aryl halides⁴⁻¹¹ provides an attractive choice for this purpose due to its more mild reaction conditions when compared to traditional methods.³ Palladium,⁵ nickel,⁶ cobalt,⁷ copper,⁸ indium,⁹ gold,¹⁰ and iron¹¹ are known to catalyze C–S bond formation. A wide array of ancillary ligands has also been used.⁴⁻¹¹ While PPh₃ was shown to be successful in the first palladium-catalyzed C-S coupling by Migita et al. in 1980,^{5a} it has received minimal attention since. When considering the mechanism of palladiumcatalyzed C-S coupling, the undesirable anionic and bridging thiolate complexes can be formed when a monophosphine is used, and this is thought to inhibit the efficiency of the catalysis by decreasing the rate of reductive elimination. Recent studies revealed that bisphosphines (Fig. 1), for example, Josiphos (1-dicyclohexylphosphino-2-di-*tert*-butylphosphinoethylferrocene, L1),^{5c-e} BINAP [2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, L2],^{5f} xantphos [9,9-dimethyl-4,5-bis(diphenylphosphino)xanthene, L3],^{5g,5h} and DPEphos [bis(2-diphenylphosphinophenyl)ether, **L4**]⁵ⁱ are more efficient than monophosphines in palladium-catalyzed S-arylation of thiols with aryl halides. Bisphosphines have also received significant attention with other metal-catalyzed reactions, for example; nickel/dppf [1,1'-bis(diphenylphosphanyl) ferrocene, L5]-⁹ and cobalt/dppe [1,2-bis(diphenylphosphino)-ethane, L6]catalyzed¹⁰ C–S bond formation.

Rhodium has been shown to be an invaluable metal for bondforming transformations;^{12–16} rhodium-catalyzed C–C,¹³ C–N,¹⁴ and C–O¹⁵ cross-coupling reactions are well-known. Despite this success, the rhodium-catalyzed C–S coupling is rare.¹⁶ Yamaguchi and co-workers reported the rhodium-catalyzed coupling disulfides with aryl fluorides, however, the system is limited to strongly electron-withdrawing aryl fluorides.^{16a} In 2005, Tanaka reported the rhodium-catalyzed reductive coupling of disulfides with alkyl halides, but there remain some drawbacks in this system. First, the substrates are limited to alkyl halides; on the other hand, the diarylthioethers are not possible to be formed by this method. Second, the preparation of disulfides in advance is required.^{16b} Thus, it is highly desirable to develop a general procedure of the rhodium-catalyzed C–S bond formation from thiols. Here, we



Figure 1. Structures of the ligands L1–L7.



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Table 1

Optimized the reaction conditions^a



4	L4	NaOtBu	Dioxane	98
5	L5	NaO <i>t</i> Bu	Dioxane	93
6	L6	NaOtBu	Dioxane	73
7	L7	NaOtBu	Dioxane	99
8	L7	KO <i>t</i> Bu	Dioxane	39
9	L7	КОН	Dioxane	20
10	L7	NaOH	Dioxane	19
11	L7	K ₃ PO ₄	Dioxane	Trace
12	L7	Cs ₂ CO ₃	Dioxane	Trace
13	L7	Et ₃ N	Dioxane	88
14	L7	NaOtBu	Toluene	99
15	L7	NaOtBu	DMF	99
16	L7	NaOtBu	DMSO	60
17 ^b	L7	NaOtBu	Dioxane	85
18 ^b	L7	NaOtBu	Toluene	98
19 ^b	L7	NaOtBu	DMF	88
20 ^{b,c}	L7	NaOtBu	Toluene	67
21 ^d	L7	NaOtBu	Toluene	78
22e	17	$N_2 O t B_{11}$	Toluene	45

^a Reaction conditions: $[RhCl(cod)]_2$ (0.01 mmol, 5 mol %), ligand (0.02 mmol, 10 mol %), 4-iodotoluene (0.24 mmol), thiophenol (0.2 mmol), base (0.4 mmol) in 0.2 mL solvent.

Toluene

28

NaOtBu

^ь 100 °С.

23^f

^c [RhCl(cod)]₂ (0.005 mmol, 2.5 mol %), ligand (0.01 mmol, 5 mol %). Cod = cyclooctadiene.

^d RhCl(PPh₃)₃ as rhodium source.

L7

^e Rh₂(OAc)₄ as rhodium source.

^f [RhCl(CO)₂]₂ as rhodium source.

report the rhodium-catalyzed cross-coupling reaction of thiols with aryl iodides in the presence of PPh_3 as a ligand, **L7**.

In order to determine the optimized reaction conditions, 4iodotoluene and thiophenol were selected as the model substrates for this reaction. Several ligands were examined and the results are summarized in Table 1. Interestingly, electron-rich and sterically hindered ligand L1, showed good reactivity, giving the product in 89% yield (Table 1, entry 1). L2 and L3 were less effective (Table 1, entries 2 and 3). L4 possesses similar electronic effects when compared with L3, however, it possesses a more flexible backbone than L1 and L3. To our delight, a 98% of isolated yield was achieved when L4 was employed (Table 1, entry 4). L5 and L6 also exhibited good reactivity resulting in 93% and 73% yields, respectively (Table 1, entries 5 and 6). A 99% of isolated yield was obtained when PPh₃, and due to cost considerations, L7 was determined to be the ligand of choice. After screening the effect of base, NaOtBu was found to be superior when compared to the other bases (Table 1, entries 8–13). A variety of solvents were examined, and the use of toluene, DMF, or dioxane, resulted in the product being formed in excellent yields (Table 1, entries 7, 14, and 15), DMSO is not a good choice for this reaction (Table 1, entry 16). At a lower temperature, interestingly, the solvent effect (Table 1, entries 17-19) shows that toluene is better than dioxane and DMF, providing the product in 98% isolated yield at 100 °C (Table 1, entry 18). It was observed that lower catalyst loadings diminished the yield of the target (Table 1, entry 20). We also examined the rhodium sources and found that [RhCl(cod)]₂ was superior to RhCl(PPh₃)₃, Rh₂(OAc)₄, [RhCl(CO)₂]₂ (Table 1, entries 21-23, respectively). Additionally, lower yields

Table 2

Rhodium-catalyzed coupling reaction of thiols with aryl iodides^a





Table 2 (continued)

Entry	Product		Yield ^b (%
16	S C ₆ H ₁₃	3q	84
17	S C ₁₂ H ₂₅	3r	84
18	MeO S C ₁₂ H ₂₅	3s	83
19	MeO	3t	98
20	MeO	3u	92
21	MeO SC6H13	3v	85
22	MeO	3w	98
23	Br SC12H25	3x	73
24	H ₂ N	Зу	55
25	S S	3z	76

^a Reaction conditions: [RhCl(cod)]₂ (0.01 mmol, 5 mol %), **L7** (0.02 mmol, 10 mol %), aryl iodide (0.24 mmol), thiol (0.2 mmol), NaOtBu (0.4 mmol) in 0.2 mL toluene.

^b Isolated yield.

were observed when 4-iodotoluene was replaced by 4-bromotoluene (7% isolated yield) or 4-chlorotoluene (trace amount of product was detected by GC–MS) under the same reaction conditions.

Based on the above results, we decided to use $5 \mod \%$ of $[RhCl(cod)]_2$ and $10 \mod \%$ of PPh_3 as the catalyst; toluene as solvent and NaOtBu as a base at $100 \degree C$ as the optimized reaction conditions for further studying the scope of this novel catalytic system. The results are summarized in Table 2. The aryl thiols (Table 2, entries 1–13) and alkyl thiols (Table 2, entries 14–25) reacted smoothly with a variety of aryl iodides, giving the products in good to excellent yields. It is important to note that the functional groups including chloro-(Table 2, entries 1 and 6), bromo-(Table 2, entries 10 and 23), trifluoromethyl (Table 2, entry 13), and free amine (Table 2, entries 11 and 24) are all tolerated during this transformation. The aryl iodides bearing electron-rich groups such as 4-iodoanisole can be coupled smoothly to provide the products in excellent yields (Table 2, entries 5–9 and 18–22).

In conclusion, we have reported the coupling reaction of rhodium-catalyzed C–S bond formation between thiols and aryl iodides by using $[RhCl(cod)]_2$ and PPh₃ as an auxiliary ligand. A broad spectrum of thiols was reacted smoothly to provide the aryl thioethers in good to excellent yields. Investigation of rhodiumcatalyzed coupling of thiols with more challenging aryl bromides and chlorides is currently under progress in our laboratory.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06. 054.

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