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Cobalt-Catalyzed Aryl–Sulfur Bond Formation

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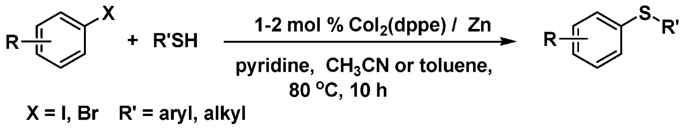
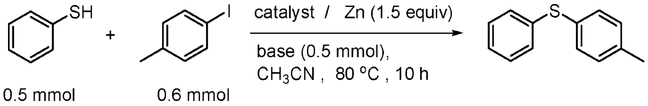
ABSTRACT



A new cobalt-catalyzed coupling of aryl halides with thiophenols and alkanethiols is reported. A variety of aryl sulfides can be prepared in excellent yields under mild reaction conditions using 1–2 mol % of CoI_2(dppe) and Zn. This new cobalt-catalyzed coupling represents an interesting addition to previously known methods to synthesize thioethers.

Transition-metal-catalyzed coupling is one of the most important tools to form a carbon−heteroatom bond.[1] Among these, the formation of the carbon−sulfur bond has received much attention due to the occurrence of this bond in many molecules that are of biological, pharmaceutical, and material interest.[2] Copper-, palladium-, and nickel-based catalysts are generally employed for this coupling reaction.[3] Although very nice methodologies are currently available, still the requirement for high-temperature, high catalyst loading or specially designed phosphine ligands has prompted a search for a better catalyst.[4] Among the alternatives, the use of cobalt as highly reactive catalysts for carbon−carbon bond-forming reactions has been recently demonstrated by Knochel, Oshima, Gosmini, and others.[5] The organometallic reagents used are based on magnesium, zinc, or copper. Our group is also interested in cobalt-catalyzed coupling reactions.[6] Very recently, we

Table 1. Optimization Studies for the Co-Catalyzed Coupling of Aryl Iodides and Thiophenols[a]



entry	catalyst	mol %	base	yield %
1	$CoI_2(PPh_3)_2$	5	pyridine	90
2	$CoI_2(PPh_3)_2$	2	pyridine	62
3	CoI_2(dppe)	5	pyridine	99
4	CoI_2(dppe)	2	pyridine	97
5	$CoCl_2$(dppe)	2	pyridine	94
6	CoI_2(dppm)	2	pyridine	80
7	CoI_2(dppb)	2	pyridine	49
8	**CoI_2(dppe)**	**1**	pyridine	**95**
9[b]	CoI_2(dppe)	1	pyridine	93
10	CoI_2	5	pyridine	trace
11	$NiCl_2$(dppe)	1	pyridine	31
12	CoI_2(dppe)	1	Et_3N	61
13	CoI_2(dppe)	1	K_2CO_3	45
14	CoI_2(dppe)	1	DIPEA	82

[a] Reaction conditions: 0.60 mmol of 4-iodotoluene, 0.50 mmol of thiophenol, 0.750 mmol of Zn, and 0.50 mmol of base in 2 mL of CH_3CN at 80 °C for 10 h. [b] 0.50 mmol of 4-iodotoluene was employed. Yields were determined by the ^1H NMR integration method using mesitylene as the internal standard.

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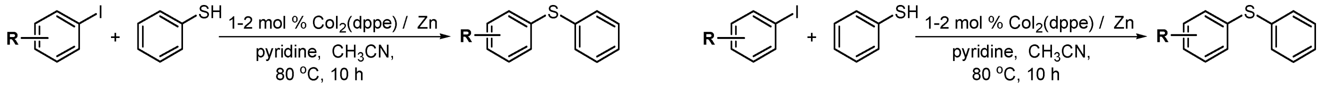
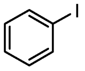
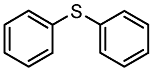
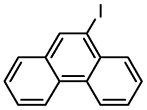
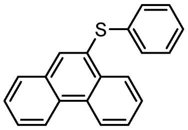
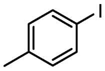
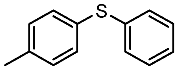
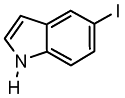
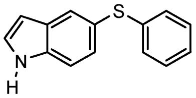
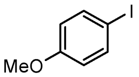
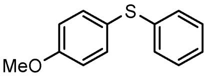
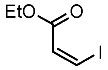
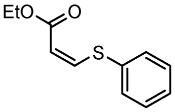
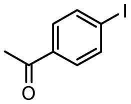
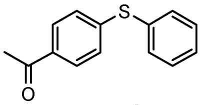
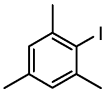
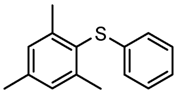
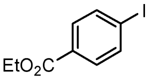
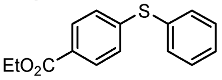
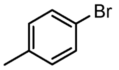
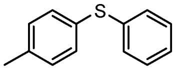
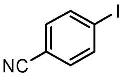
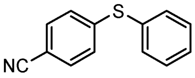
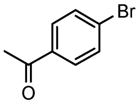
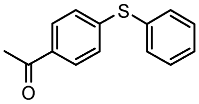
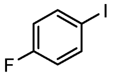
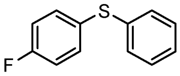
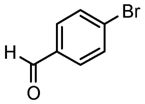
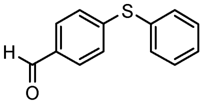
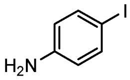
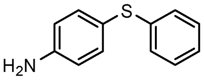
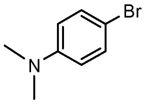
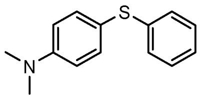
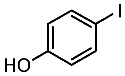
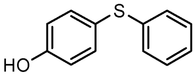
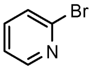
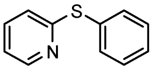
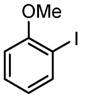
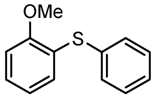
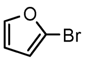
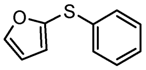
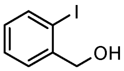
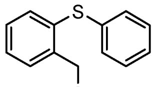
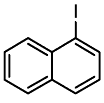
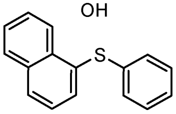
Table 2. Results of Co-Catalyzed Coupling of Aryl Halides and Thiophenol[a]



entry	aryl halide	aryl sulfide	isolated yield %	entry	aryl halide	aryl sulfide	isolated yield %
1			98	13			99
2			93	14			96
3			90	15			88
4			98	16			29
5			97	17			94
6			84	18			91
7			94	19			70
8			90	20			99
9			96	21[b]			64
10			84	22			82
11			92				
12			97				

[a] Reaction conditions: 0.50 mmol of aryl halide, 0.50 mmol of thiophenol, 0.0050 mmol of CoI_2(dppe), 0.750 mmol of Zn, and 0.50 mmol of pyridine in 2 mL of CH_3CN at 80 °C for 10 h. For arylbromides, 0.010 mmol of CoI_2(dppe) was used. [b] DIPEA was used instead of pyridine, and 2 equiv of 2-bromopyridine was used.

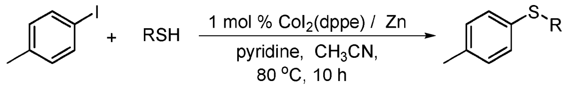
reported a reductive coupling of saturated alkyl halides with activated alkenes to form Csp^3-Csp^3 bonds.[7] Herein, we wish to report that a cobalt-based catalyst can catalyze the formation of aryl−sulfur bonds in a very efficient manner. In a preliminary reaction, 4-iodotoluene was treated with thiophenol in the presence of 5 mol % of $CoI_2(PPh_3)_2$, zinc, and pyridine in acetonitrile for 10 h; the corresponding diaryl sulfide was obtained in 90% yield (Table 1, entry 1). To the best of our knowledge, this is the first cobalt-catalyzed coupling of aryl halides and thiols to form aryl sulfides.

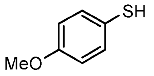
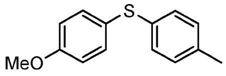
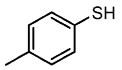
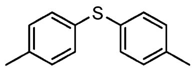
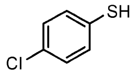
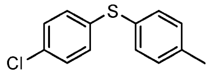
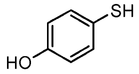
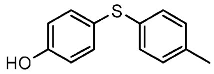
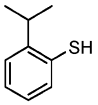
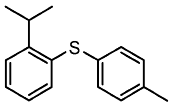
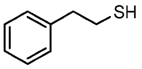
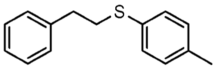
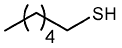
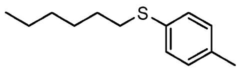
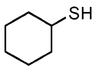
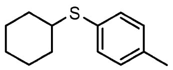
To optimize the reaction conditions as well as to reduce the catalyst loading, we first tried different cobalt catalysts (Table 1). Reducing the amount of $CoI_2(PPh_3)_2$ reduced the yield drastically (entry 2). Then, we tried a simple series of bidentate ligands with different combinations of halides (entries 3−9). CoI_2(dppe) was found to be a very effective catalyst for this coupling reaction (entry 3). To our delight, the reduction of the catalyst loading did not reduce the yield significantly (entries 4 and 8). Phosphine-free CoI_2 was ineffective for the present reaction (entry 10). The use of nickel as a catalyst gave a low yield (entry 11). Other bases were also effective. The use of Et_3N as base instead of pyridine with 1 mol % of CoI_2(dppe) gave the diarylsulfide in 61% yield (entry 12). K_2CO_3 also worked, with a yield of 45% (entry 13). When DIPEA was used as base, the coupling occurred in 82% yield.

To explore the scope of the present reaction, we examined different aryl halides (Table 2). Both an electron-donating group and an electron-withdrawing group at the para position of aryl iodides reacted with thiophenol (1 equiv) in the presence of pyridine (1 equiv), 1 mol % of CoI_2(dppe), and Zn powder (1.5 equiv) in acetonitrile to give the corresponding aryl sulfides in very good yields (entries 2−7). Under the same reaction conditions, 4-iodoaniline and 4-iodophenol also reacted well to give aryl sulfides in excellent yields (entries 8 and 9). Substitution at the ortho position did not affect the reaction. Thus, when 2-iodobenzylalcohol was employed, the product was formed in 92% yield (entries 10 and 11). 1-Iodonaphthalene and 9-iodophenanthrene also worked equally well for this reaction (entries 12 and 13). Heteroaryl iodide underwent a coupling reaction with thiophenols (entry 14). Vinyl iodide underwent the coupling reaction with preservation of the cis stereochemistry in 88% yield (entry 15). Sterically hindered mesityl iodide coupled only with a modest yield of 27% (entry 16). Aryl bromides also worked well for this coupling reaction (entries 17−22), although in these cases 2 mol % of the cobalt catalyst was employed. Importantly, 2-bromopyridine gave the corresponding heteroaryl sulfide in good yield (entry 21), and 2-bromofuran also coupled smoothly (entry 22).

By using the same protocol, we were also able to couple aryl halides with various substituted thiophenols (Table 3, entries 1−5). Interestingly, when 4-mercaptophenol was employed, the coupling of the C−S bond took place very efficiently (entry 4). 2-Isopropyliodobenzene also gave the corresponding aryl sulfides in very good yields (entry 5). Further, our methodology can be extended to the coupling of various aryl halides with alkanethiols in excellent yields (entries 6−8). It is noteworthy that in these reactions toluene is much more effective than acetonitrile as the solvent. However, the reason for the difference in product yield in different solvents is not clear.

Table 3. Results of Co-Catalyzed Coupling of 4-Iodotoluene with Thiophenols and Alkanethiols[a]



entry	thiol	aryl sulfide	isolated yield %
1			96
2			99
3			93
4			99
5			91
6[b]			96
7[b]			89
8[b]			91

[a] Reaction conditions: 0.50 mmol of 4-iodotoluene, 0.50 mmol of thiophenol or 0.50 mmol of alkanethiol, 0.0050 mmol of CoI_2(dppe), 0.750 mmol of Zn, and 0.50 mmol of pyridine in 2 mL of CH_3CN at 80 °C for 10 h. [b] Toluene was used instead of CH_3CN at 70 °C.

Even though a more detailed study is required to completely understand the mechanistic rationale of this cobalt-catalyzed coupling sequence, a tentative pathway can be proposed. Reduction of Co(II) to Co(I) by zinc dust initiates the catalysis (Scheme 1). The coupling may start with a coordination of the thiolate to the cobalt(I) center, followed by an oxidative addition of aryl halides to Co(I). Carbon−sulfur reductive elimination would afford the thioether and regenerate the Co(I) catalyst. We believe that the facile reaction of the aryl iodides and bromides, especially those possessing electron-donating groups, is due to the coordination of thiolate to the Co center.[8] Here, pyridine might also act as a ligand in addition to being a base. However, an alternative pathway via oxidative addition of aryl halides to Co(I), followed by coordination of the thiolate to the Co(III) center, cannot be completely ruled out.

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(3) For Cu-catalyzed coupling of aryl halides and thiols, see: (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) Deng, W.; Zou, Y.; Wang, Y.-F.; Liu, L.; Guo, Q.-X. *Synlett* **2004**, 1254. For other Cu-catalyzed syntheses of thioethers, see: (f) Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E.; *Tetrahedron Lett.* **2000**, *41*, 1283. (g) Savarin, C.; Srogl, J.; Liebeskind, L. S. *Org. Lett.* **2002**, *4*, 4309. (h) Herradura, P. S.; Pendola, K. A.; Guy, R. K. *Org. Lett.* **2000**, *2*, 2019. For Pd-catalyzed reactions, see: (i) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253. (j) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (k) Fernández Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (l) Murata, M.; Buchwald, S. L. *Tetrahedron* **2004**, *60*, 7397. (m) Schopfer, U.; Schlapbach, A. *Tetrahedron* **2001**, *57*, 3069. (n) Li, G. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1513. For Ni-catalyzed reactions, see: (o) Cristau, H. J.; Chabaud, B.; Chêne, A.; Christol, H. *Synthesis* **1981**, 892. (p) Millois, C.; Diaz, P. *Org. Lett.* **2000**, *2*, 1705. (q) Percec, V.; Bae, J. Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895. (r) Takagi, K. *Chem. Lett.* **1987**, 2221.

(4) (a) Lindley, J. *Tetrahedron* **1984**, *40*, 1433. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.

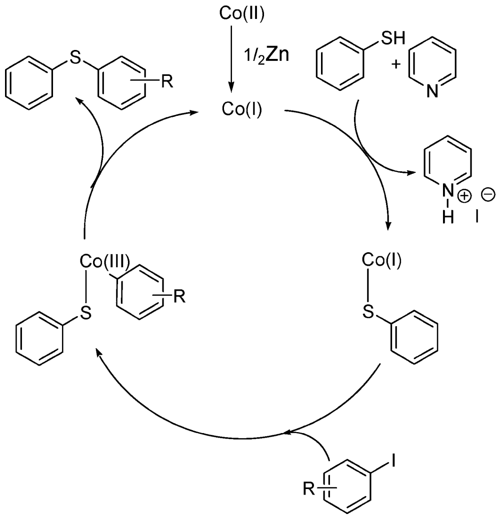
(5) (a) Yorimitsu, H.; Oshima, K. *Pure Appl. Chem.* **2006**, *78*, 441. (b) Ohmiya, H.; Wakabayashi, K.; Yorimitsu, H.; Oshima, K. *Tetrahedron* **2006**, *62*, 2207. (c) Shinokubo, H.; Oshima, K. *Eur. J. Org. Chem.* **2004**, *10*, 2081. (d) Korn, T. J.; Schade, M. A.; Wirth, S.; Knochel, P. *Org. Lett.* **2006**, *8*, 725. (e) Amatore, M.; Gosmini, C.; Perichon, J. *J. Org. Chem.* **2006**, *71*, 6130. (f) Kazmierski, I.; Gosmini, C.; Paris, J.-M.; Perichon, J. *Synlett* **2006**, *6*, 881. (g) Korn, T. J.; Cahiez, G.; Knochel, P. *Synlett* **2003**, *12*, 1892.

(6) (a) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Chem. Commun.* **2005**, *39*, 4955. (b) Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. *J. Org. Chem.* **2004**, *69*, 4781. (c) Chang, K.-J.; Rayabarapu, D. K.; Cheng, C.-H. *Org. Lett.* **2003**, *5*, 3963.

(7) (a) Shukla, P.; Hsu, Y. -C.; Cheng, C. -H. *J. Org. Chem.* **2006**, *71*, 655. See also: (b) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *J. Am. Chem. Soc.* **2002**, *124*, 9696. (c) Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *Tetrahedron Lett.* **2004**, *45*, 6203.

(8) The reactivity of aryl bromides and aryl iodides with electron-donating substituents was not found to be remarkable with this catalyst system under reaction conditions similar to those reported earlier in our labortories. See ref 6b.

Scheme 1



In comparison with the reported Cu-, Pd-, and Ni-catalyzed syntheses of thioethers via the coupling of aryl halides and thiols, the present method offers a very interesting alternative. Most Cu-catalyzed reactions usually require high catalyst loading and high reaction temperatures.[3a−e,9] Cobalt salts are also less expensive and require only very low catalyst loading. This cobalt-catalyzed reaction employs a simple phosphine ligand and does not call for the use of very bulky ligands, thereby offering a good complement to Pd- and Ni-catalyzed reactions.[3i−r]

In summary, we have described the first cobalt-catalyzed coupling of aryl halides with thiols to form aryl sulfides under mild reaction conditions in excellent yields. This new coupling reaction underlines the potential of using cobalt as a very user-friendly, inexpensive, and efficient catalyst for coupling of carbon−heteroatom as well as carbon−carbon bonds. Further studies along these lines are underway in our laboratories.

Acknowledgment. We thank the National Science Council of the Republic of China (NSC 95-2119-M-007-005) for support of this research.

Supporting Information Available: General experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[9] However, recently there has been improvement in the Cu-catalyzed synthesis of thioethers. The catalyst loading has been decreased up to 5 mol % at reaction temperatures of 80 °C. See ref 3b.