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Synthesis of Functionalized Diaryl Sulfides by Cobalt-Catalyzed Coupling between Arylzinc Pivalates and Diaryl Disulfides

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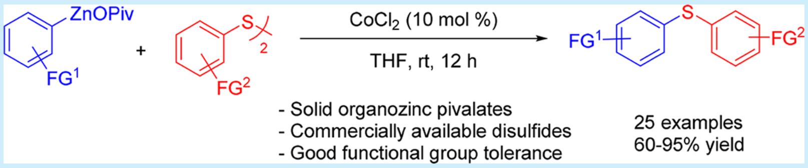
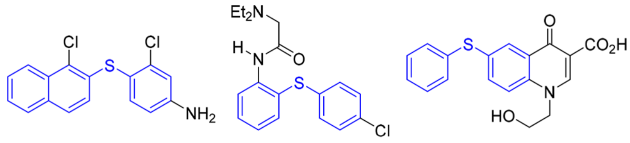
Supporting Information



ABSTRACT: An efficient protocol for the cobalt-catalyzed preparation of diaryl sulfides from solid organozinc pivalates and commercially available diaryl disulfides is reported. This cross-coupling proceeds at room temperature and displays a good functional group tolerance, allowing the preparation of a diversity of symmetrical or asymmetrical diaryl sulfides in 60−95% yield.

Diaryl sulfides are important intermediates in the synthesis of natural products[1] and pharmaceuticals.[2] The diaryl sulfide **1**, for example, is a LFA-1/CAM-1 antagonist, **2** is an anti-inflammatory agent, and **3** is an HIV-1 integrase inhibitor (Figure 1).[2] In addition, diaryl sulfides have been used in the synthesis of several new organic materials, e.g., semiconductors.[3] Moreover, they can serve as ligands in transition-metal-catalyzed reactions.[4] Therefore, efficient protocols for the C_{aryl}−S bond formation are highly desirable. Transition-metal-catalyzed C_{aryl}−S cross-coupling reactions using Pd,[5] Ni,[6] Fe,[7] Co,[8] In,[9] and Cu[10] catalysis have been reported for the preparation of diaryl thioethers from aryl halides and aryl thiols or using C−H activation.[11] In addition, organomagnesium halide mediated preparations of diaryl sulfides or S_NAr reactions on electron-poor systems have been reported.[12] Though efficient, these methods often require high temperature[13] and specially designed ligands[14] or are not compatible with many functional groups such as an ester or a nitrile,[12a] which limit their applications. Recently, we have reported the preparation of highly functionalized solid organozinc pivalates with improved air and moisture stability, which readily undergo cross-coupling reactions.[15] In particular, the combination of organozinc pivalates and cobalt catalysis has proven to be of interest because of a rate enhancement due to the presence of the pivalate ion.[16]

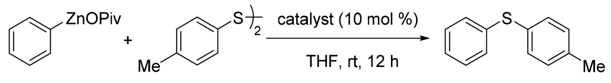


1 LFA-1/ICAM-1 antagonists
2 anti-inflammatory agent
3 HIV-1 integrase inhibitor

Figure 1. Bioactive diaryl disulfides.

Herein, we report the cobalt-catalyzed[17] synthesis of diaryl sulfides, starting from organozinc pivalates and commercially available diaryl disulfides using $CoCl_2$ as catalyst in the absence of any additional ligand. In preliminary experiments, phenylzinc pivalate (**4a**)[18] was treated with *p*-tolyl disulfide (**5a**) in THF at room temperature for 12 h under various conditions (Table 1). First, several standard transition-metal catalysts

Table 1. Optimization of the Reaction Conditions for the Cobalt-Catalyzed Reaction between Organozinc Pivalates and Diaryl Disulfides



4a (1.5 equiv) **5a** (1.0 equiv) **6a**

entry	catalyst	ligand[a]	yield[b] (%)
1	$FeCl_2$		0
2	$PdCl_2$		0
3	$CuCl_2$		30
4	$NiCl_2$		30
5	$CoCl_2$		87 (79)[c]
6	$CoBr_2$		85
7	$Co(acac)_2$		79
8	$Co(OAc)_2$		55
9	$CoCl_2$		75[d]
10	$CoCl_2$		75[e]
11	$CoCl_2$	**L1**	74

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Table 1. continued

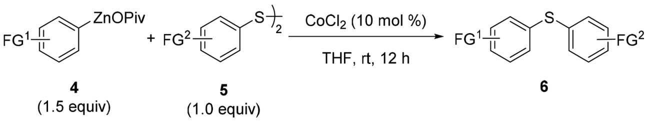
entry	catalyst	ligand[a]	yield[b] (%)
12	$CoCl_2$	**L2**	12
13	$CoCl_2$	**L3**	22
14	$CoCl_2$	**L4**	51
15	$CoCl_2$		89[f]

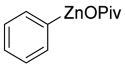
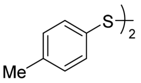
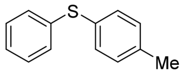
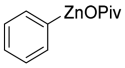
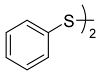
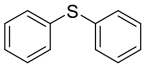
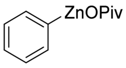
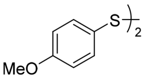
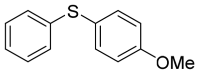
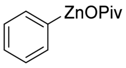
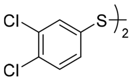
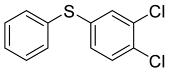
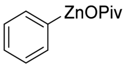
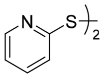
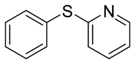
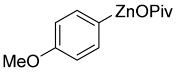
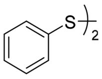
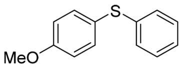
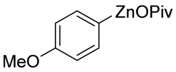
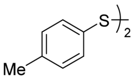
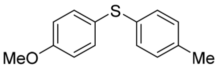
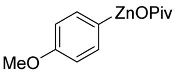
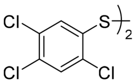
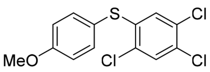
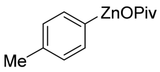
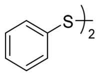
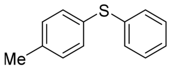
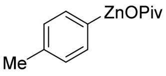
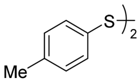
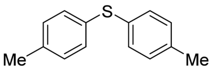
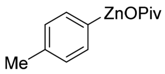
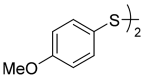
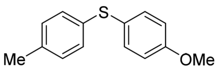
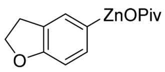
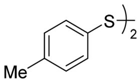
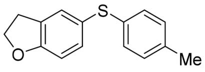
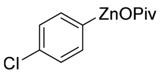
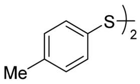
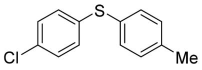
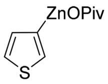
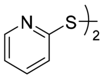
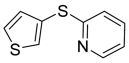
[a] Using 20 mol % of the ligands. [b] Calibrated GC yield using dodecane as internal standard. [c] Isolated yield. [d] Using 5 mol % of $CoCl_2$. [e] Using 20 mol % of $CoCl_2$. [f] $CoCl_2$ (99.99% purity) was used.

were tested. $FeCl_2$, $PdCl_2$, $CuCl_2$, and $NiCl_2$ were not suitable for the reaction since yields did not exceed 30% (entries 1–4). However, when $CoCl_2$ (10 mol %) was used, the diaryl sulfide **6a** was obtained in 87% yield (entry 5). Other cobalt sources such as $CoBr_2$, $Co(acac)_2$, or $Co(OAc)_2$ did not lead to an improved reaction outcome (entries 6–8). Decreasing or increasing the catalyst loading to 5 or 20 mol % did not lead to higher yields (entries 9 and 10). In addition, the addition of several ligands such as DMEDA (1,2-dimethylethylenediamine, **L1**), 2,2′-bipyridine (**L2**), 1,10-phenanthroline (**L3**), or triphenylphosphine (**L4**) did not have a beneficial effect (entries 11–14). Furthermore, changing the solvent to dioxane or acetonitrile did not provide higher yields.[19] Additionally, it was verified that no other metal contaminations are responsible for this catalysis: Thus, using $CoCl_2$ (99.99% purity) led to **6a** in 89% yield (entry 15).

With these optimized reaction conditions in hand, a range of cobalt-catalyzed reactions between organozinc pivalates of type **4** and diaryl disulfides of type **5** were performed, leading to several diaryl sulfides of type **6** (Table 2). Thus, various diaryl disulfides, including diphenyl disulfide (**5b**) and bis(4-methoxyphenyl) disulfide (**5c**), reacted with phenylzinc

Table 2. Cobalt-Catalyzed Reactions between Various Organozinc Pivalates of Type 4 and Diaryl Disufides of Type 5



entry	organozinc 4	disulfide	thioether 6 (yield[a])
1	 **4a**	 **5a**	 **6a**: 79%
2	 **4a**	 **5b**	 **6b**: 78%
3	 **4a**	 **5c**	 **6c**: 95%
4	 **4a**	 **5d**	 **6d**: 81%
5	 **4a**	 **5e**	 **6e**: 92%
6	 **4b**	 **5b**	 **6f**: 75%
7	 **4b**	 **5a**	 **6g**: 84%
8	 **4b**	 **5f**	 **6h**: 78%
9	 **4c**	 **5b**	 **6i**: 75%
10	 **4c**	 **5a**	 **6j**: 79%
11	 **4c**	 **5c**	 **6k**: 91%
12	 **4d**	 **5a**	 **6l**: 85%
13	 **4e**	 **5a**	 **6m**: 66%
14	 **4f**	 **5e**	 **6n**: 71%

[a] Isolated yield of analytically pure products.

DOI: 10.1021/acs.orglett.8b03319
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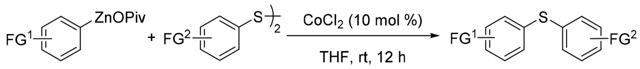
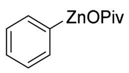
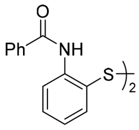
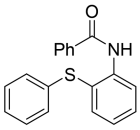
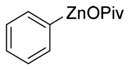
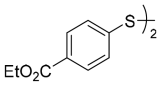
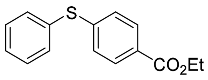
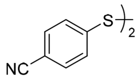
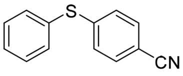
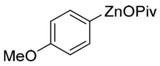
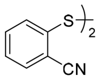
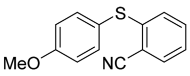
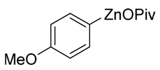
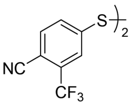
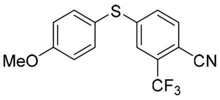
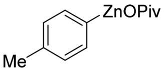
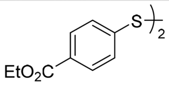
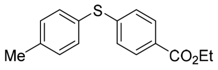
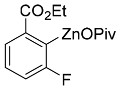
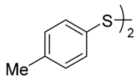
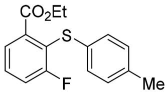
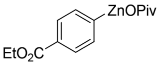
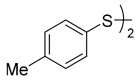
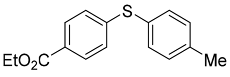
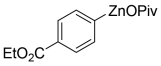
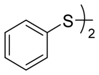
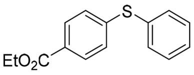
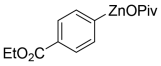
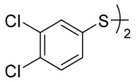
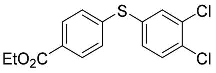
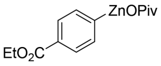
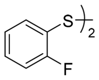
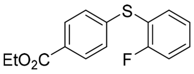
Table 3. Cobalt-Catalyzed Reactions between Various Organozinc Pivalates of Type 4 and Diaryl Disufides of Type 5 Bearing Sensitive Functional Groups



4 (1.5 equiv) **5** (1.0 equiv) **6**

Entry	organozinc **4**	disulfide	thioether **6** (Yield[a])
1	 **4a**	 **5g**	 **6o**: 60%
2	 **4a**	 **5h**	 **6p**: 66%
3	 **4a**	 **5i**	 **6q**: 60%
4	 **4b**	 **5j**	 **6r**: 71%
5	 **4b**	 **5k**	 **6s**: 80%
6	 **4c**	 **5h**	 **6t**: 65%
7	 **4g**	 **5a**	 **6u**: 81%
8	 **4h**	 **5a**	 **6v**: 79%
9	 **4h**	 **5b**	 **6w**: 68%
10	 **4h**	 **5d**	 **6x**: 71%
11	 **4h**	 **5l**	 **6y**: 60%

[a] Isolated yield of analytically pure products.

pivalate (**4a**) to give the diaryl sulfides **6a–c** in 78–95% yield (Table 2, entries 1–3). Reaction of phenylzinc pivalate (**4a**) with the halogenated disulfide **5d** or dipyridyl disulfide (**5e**) gave the disulfides **6d–e** in 81–92% yield (entries 4 and 5).

In addition, electron-rich anisylzinc pivalate (**4b**) reacted with several disulfides, including the electron-poor trihalogenated disulfide **5f**, leading to the sulfides **6f–h** in 75–84% yield (entries 6–8). When tolylzinc pivalate (**4c**), 5-benzofurylzinc pivalate (**4d**), or 4-chlorophenylzinc pivalate (**4e**) was used in the coupling reaction with diaryl disulfides, the diaryl sulfides **6i–m** were isolated in 66–91% yield (entries 9–13). Reaction of the heteroarylzinc pivalate **4f** with dipyridyl disulfide (**5e**) gave the diheterocyclic sulfide **6n** in 71% yield (entry 14). However, other electron-poor heteroaryl zinc pivalates only afforded the corresponding thioethers in traces.[19]

Next, several organozinc pivalates of type **4** and diaryl disulfides of type **5** bearing sensitive functional groups were employed in the coupling reaction. Thus, phenylzinc pivalate (**4a**) reacted with the disulfide **5g** bearing an amide functionality. Remarkably, the amide did not inhibit the reaction from proceeding, which resulted in the formation of the sulfide **6o** in 60% yield (Table 3, entry 1). Other diaryl disulfides bearing an ester or a nitrile group (**5h–k**) were also suitable for this coupling reaction, leading to the sulfides **6p–t** in 60–80% yield (entries 2–6). When the organozinc pivalate **4g**, which was prepared via directed metalation using TMPMgCl·LiCl[20] followed by transmetalation using Zn(OPiv)$_2$,[19] was employed in the reaction, the sulfide **6u** was obtained in 81% yield (entry 7). Additionally, the organozinc pivalate **4h**, bearing an ester functionality, led to the sulfides **6v–y** in 60–79% yield (entries 8–11).

In summary, a cobalt-catalyzed C(sp^2)–S bond formation, using organozinc pivalates and commercially available diaryl disulfides, is reported. Various electron-rich and electron-poor organozinc pivalates were suitable substrates for the reaction protocol. Also, several sensitive functional groups including an ester, a nitrile, or an amide were tolerated in the reaction. An investigation of the reaction mechanism is currently underway in our laboratories.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03319.

Full experimental details; ^{1}H and ^{13}C spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(19) See the Supporting Information for further details.

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