JOC*Note*

Alkyl- or Arylthiolation of Aryl Iodide via Cleavage of the S−S Bond of Disulfide Compound by Nickel Catalyst and Zinc

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Abstract: Various aryl sulfides can be synthesized by nickel-catalyzed alkyl- or arylthiolation of aryl iodide with a disulfide compound. This reaction produces Ni(0) from $NiBr_2$−bpy by the reduction with zinc, and this generated complex works as an activating species to convert ArI into ArSR under neutral conditions. Furthermore, this system enables the use of two RS groups in $(RS)_2$.

The transition metal-catalyzed thiolation of aryl halide is an important reaction in the synthesis of miscellaneous unsymmetrical aryl sulfides.[1] These aryl sulfides have interesting characteristics in organic compounds and are often used as effective reagents or convenient intermediates in organic synthesis.[2] Usually, in methods for the metal-catalyzed preparation of aryl sulfides, the cross-coupling of thiol with aryl halide, using a copper or palladium catalyst under basic conditions, is used.[3] However, the metal-catalyzed thiolation of aryl halide with a disulfide compound has rarely been done, despite of the fact that the efficient use of $(RS)_2$ in the catalytic thiolation of alkyl halide has been published.[4]

As a rule, a transition metal rapidly inserts into a disulfide bond,[5] and the formed complex $(RY)_2M$ prevents the reaction, such as the thiolation of aryl halide, owing to the stability of a metal−chalcogen bond. To solve this problem, it is necessary for $(RY)_2M$ to be reduced into a mono(organochalcogenide)−metal complex RYM (Figure 1).

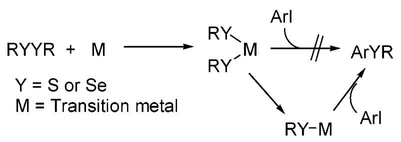

FIGURE 1. Strategy for the synthesis of ArSR from ArI and $(RS)_2$.

Recently, we found that the addition of magnesium stimulates the copper-catalyzed synthesis of diaryl chalcogenide from diphenyl dichalcogenide and aryl iodide.[6] Two points are noted in this reaction: (1) the copper catalyst is reduced by magnesium and (2) it is possible to use two PhY (Y = S or Se) groups in diphenyl dichalcogenide under neutral conditions.

On the other hand, the above-described method has been limited to the case of a Cu(I)−Mg system, and in the use of dialkyl dichalcogenide, a lowering of the reactivity is often observed.

In the present Note, we report a nickel-catalyzed synthesis of unsymmetrical aryl sulfide from aryl iodide and dialkyl- or diaryl-disulfide using zinc.

The nickel-catalyzed thiolation of aryl halide with thiol under basic conditions has been well studied.[7] Similarly, in the presence of polymer-supported borohydride, the phenylselenation of aryl halide with diselenide is reported by Millois and Diaz.[8] Ni-catalyzed thiolation that uses disulfide is briefly described in their Note. Their method involved the generation of $PhSe^-$ ($PhSeB(OEt)_3^-$) by the reduction of $(PhSe)_2$ using borohydride in EtOH−THF.[9] However, a catalytic system that uses a property that nickel metal inserts into the disulfide bond has not been researched. To carry out the reaction with the nickel catalyst and disulfide, we first investigated the addition of various metals as reductive reagents of nickel (Table 1).

From many experimental results, it was obvious that the addition of zinc gave a respectable yield (Table 1, entries 5, 6, and 7), but no other metals (Mg, Al, and Sn) showed any effect (Table 1, entries 2, 3, and 4). When iodobenzene (**1a**) (0.3 mmol) and diphenyl disulfide (**2a**) (0.15 mmol) were treated with $NiBr_2$−bpy (1:1, 10 mol %) and zinc (0.6 mmol) in DMF (0.5 mL) at 110 °C for 18 h, diphenyl sulfide (**3aa**) could be obtained in 90% yield (Table 1, entry 5). When the use of $NiCl_2$ or NiI_2 was examined, the yield of **3aa** was slightly lower (Table 1, entries 6 and 7). Accordingly, the employment of zinc as

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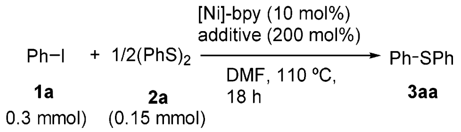
10.1021/jo040184q CCC: $27.50

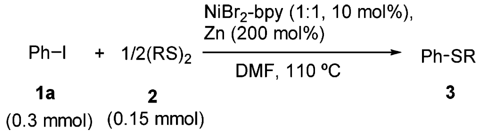
TABLE 1. Nickel-Catalyzed Phenylthiolation of 1a



entry	[Ni]	additive	**3aa** (%)[a]
1	$NiBr_2$	none	0
2	$NiBr_2$	Mg	0
3	$NiBr_2$	Al	0
4	$NiBr_2$	Sn	0
5	$NiBr_2$	Zn	90
6	$NiCl_2$	Zn	67
7	NiI_2	Zn	85

[a] Isolated yields after silica gel chromatography.

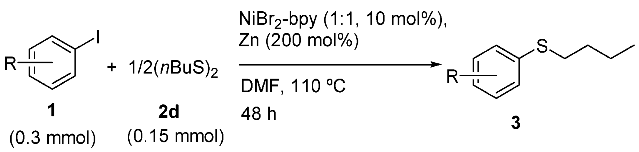
TABLE 2. Nickel-Catalyzed Coupling of 1a with $(RS)_2$



entry	$(RS)_2$ (**2**)	time (h)	PhSR	**3** (%)[a]
1	$(PhS)_2$ (**2a**)	18	**3aa**	90
2	$(4\text{-}MeC_6H_4S)_2$ (**2b**)	18	**3ab**	87
3	$(MeS)_2$ (**2c**)	72	**3ac**	80
4	(nBuS)$_2$ (**2d**)	48	**3ad**	81
5	(iPrS)$_2$ (**2e**)	72	**3ae**	68
6	(tBuS)$_2$ (**2f**)	48	**3af**	trace

[a] Isolated yields after silica gel chromatography.

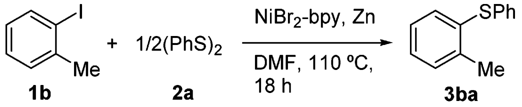
TABLE 3. Nickel-Catalyzed Coupling of ArI and (nBuS)$_2$



entry	ArI (**1**)	ArSnBu	**3** (%)[a]
1	C_6H_5I (**1a**)	**3ad**	81
2	2-MeC_6H_4I (**1b**)	**3bd**	76
3	2-$MeOC_6H_4I$ (**1c**)	**3cd**	92
4	2-$H_2NC_6H_4I$ (**1d**)	**3dd**	85
5	2-HOC_6H_4I (**1e**)	**3ed**	80
6	4-MeC_6H_4I (**1f**)	**3fd**	85
7	4-$MeOC_6H_4I$ (**1g**)	**3gd**	75
8	4-BrC_6H_4I (**1h**)	**3hd**	76
9	4-ClC_6H_4I (**1i**)	**3id**	80
10	4-$F_3CC_6H_4I$ (**1j**)	**3jd**	77
11	4-$H_2NC_6H_4I$ (**1k**)	**3kd**	74
12	4-HOC_6H_4I (**1l**)	**3ld**	73
13	4-$HO_2CC_6H_4I$ (**1m**)	**3md**	61
14	4-$MeO_2CC_6H_4I$ (**1n**)	**3nd**	87
15	4-AcC_6H_4I (**1o**)	**3od**	72
16[b]	*trans*-PhCH=CHBr (**1p**)	**3pd**	78
17[c]	4-$O_2NC_6H_4I$ (**1q**)	**3qd**	0

[a] Isolated yields after silica gel chromatography. [b] nBu$_4$NI was added, 10 mol %. [c] **1q** was recovered in 96% yield.

SCHEME 1. Effect of Nickel Bromide and Zinc



NiBr$_2$-bpy (1 : 1) (mol%)	Zn (mol%)	**3ba** (%)	**1b** (%)	**2a** (%)
none	200	0	97	96
10	none	0	98	97
100	none	0	97	97

the reductant was the most suitable for the nickel-catalyzed thiolation of aryl iodide.

The thiolation of **1a** with different disulfides **2** was then examined. As shown in Table 2, a mixture of **1a**, **2**, NiBr$_2$−bpy catalyst, and zinc in DMF was treated at 110 °C. In the reaction of diaryl disulfides, the corresponding sulfides **3** were available in good yields (Table 2, entries 1 and 2). Similarly, this coupling can also take advantage of the use of dialkyl disulfides (Table 2, entries 3, 4, and 5). For instance, the case of di-n-butyl disulfide (**2d**) provides **3ad** in 81% yield (Table 2, entry 4). Regrettably, when di-*tert*-butyl disulfide (**2f**) was used, the reactivity was significantly decreased (Table 2, entry 6).

Next, the coupling of ortho- or para-substituted aryl iodides with di-n-butyl disulfide (**2d**) was carried out according to established methods. The results of the preparation of aryl n-butyl sulfides are presented in Table 3. The desired sulfides **3** could be produced in 61−92% yields by aryl iodides **1** having various functional groups, and di-n-butyl disulfides (**2d**) were treated with NiBr$_2$−bpy catalyst and zinc in DMF at 110 °C for 48 h (Table 3, entries 1−15). Moreover, this reaction could result in n-butyl styryl sulfide (**3pd**) in 78% yield from *trans*-2-bromostyrene (**1p**) by the addition of n-Bu$_4$NI (10 mol %) (Table 3, entry 16).[12a] Unfortunately, 4-nitro-1-iodobenezene (**1q**) could not convert into the corresponding product, and **1q** was recovered in 96% yield (Table 3, entry 17). Thus, the combination of the nickel catalyst and zinc enabled the synthesis of the unsymmetrical sulfide from aryl iodide and dialkyl disulfide under neutral conditions.

This catalytic process requires a nickel salt and zinc, and it is clear that neither Ni(II)Br$_2$−bpy nor zinc itself had the ability to insert into S−S or Ar−I (Scheme 1).[10] On the contrary, Ni(0) can insert into these bonds.[11,12] The reaction of 2-iodoanisole (**1c**) in the system of the nickel−catalyst and zinc affords the biaryl and anisole in yields of 12% and 41%, respectively (Scheme 2). In addition, it has been reported widely that the Ni(II)(SR)$_2$ complex is produced by Ni(0) insertion into the disulfide bond.[11]

These facts show that, in the thiolation of aryl iodide, at the first step, an Ni(0)-species is formed by the reduction by zinc. At the next step, this Ni(0)-species

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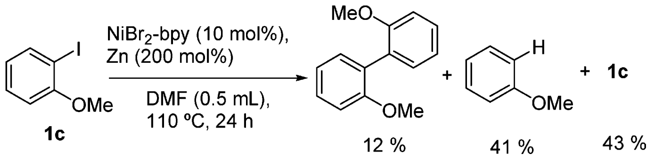
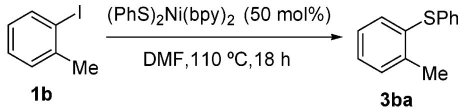
SCHEME 2. Reaction of 1c with $NiBr_2$−bpy Catalyst and Zinc



SCHEME 3. Phenylthiolation of 1b with $(PhS)_2Ni(bpy)_2$



Zn	**3ba** (%)
none	trace
200 mol%	92

inserts into S−S or Ar−I bonds, and $(RS)_2$Ni(II)[11] or ArNi(II)I[12] is produced.

It is worth noting that $(RS)_2$Ni(II) alone cannot transform ArI to ArSR. Actually, $(PhS)_2$Ni(II)$(bpy)_2$ is unavailable for the synthesis of ArSR (Scheme 3).[7c,13] However, the addition of zinc as the reductive reagent, in the presence of $(PhS)_2$Ni(II)$(bpy)_2$ (0.15 mmol), could afford phenyl 2-tolyl sulfide (**3ba**) in a 92% yield (Scheme 2). Given these results, it is presumed that (RS)Ni(I) is an activating species for the thiolation, and it is impossible to promote the reaction under this condition by using $(RS)_2$Ni(II). Similarly, it appears that ArNi(II)I is also reduced to ArNi(I) by zinc.[12] Hence, it is anticipated that the nickel-catalyzed thiolation of aryl iodide with disulfide is accelerated by (RS)Ni(I) or ArNi(I).

From these results, the reaction mechanism is considered as follows (Figure 2). After Ni(II)Br_2L is reduced to Ni(0)L (**5**) by zinc, $(RS)_2$Ni(II)L (**6**) or ArNi(II)IL (**9**) is produced via the insertion of **5** into S−S or Ar−I. It seems that the generating proportion of **6** or **9** is different according to the kind of substrate.

In catalytic cycle A, the reduction of **6** by zinc gives (RS)Ni(I)L (**7**). Subsequently, the reaction of **7** and ArI generates ArSR and Ni(I)IL via the formation of the intermediate **8**. Moreover, $Zn(SR)_2$, which was formed when **6** was reduced, yields **7** by a ligand exchange with Ni(I)X. As a consequence, this process enables the consumption of two RS groups in $(RS)_2$.

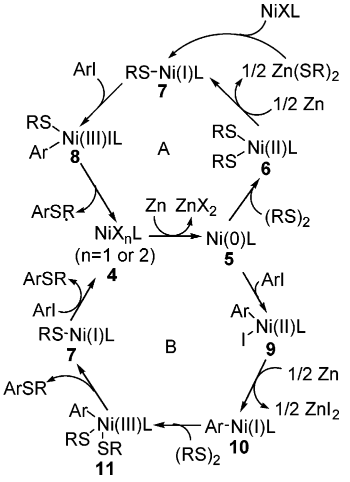


FIGURE 2. Plausible reaction mechanism.

On the other hand, in another cycle B, after the intermediate **9** is reduced to ArNi(I)L (**10**) by zinc, Ar$(RS)_2$Ni(III)L (**11**) is constructed by the oxidative addition of disulfide to **10**; at the next step, **11** provides ArSR and **7** by the reductive elimination. Finally, the complex **7** converts ArI into ArSR and also gives Ni(I)IL.

Therefore, this nickel-catalyzed thiolation of aryl iodide with disulfide proceeds through two catalytic cycles.

In conclusion, we have developed a nickel-catalyzed synthesis of unsymmetrical aryl sulfides from various aryl iodides and dialkyl- or diaryl-disulfide by the addition of zinc in one pot using the insertion of a nickel catalyst into the disulfide bond. This method can efficiently use two RS groups in the $(RS)_2$ molecule and can be carried out under neutral conditions.

Experimental Section

Typical Procedure. To a mixture of $NiBr_2$ (6.6 mg, 0.03 mmol), bpy (4.7 mg, 0.03 mmol), zinc (dust) (39.2 mg, 0.6 mmol), and DMF (0.5 mL) were added 2-iodotoluene (**1b**) (65.4 mg, 0.3 mmol) and di-*n*-butyl disulfide (**2d**) (26.8 mg, 0.15 mmol), and the mixture was stirred at 110 °C for 48 h. After evaporation of the solvent, the residue was dissolved in Et_2O, and the resulting mixture was filtered through a Celite pad. The solution was washed with H_2O and saturated sodium chloride and dried over anhydrous magnesium sulfate. Chromatography on silica gel (hexane) gave *n*-butyl 2-tolyl sulfide (**3bd**)[3g] (45.3 mg, 76%). ^1H NMR ($CDCl_3$) δ 0.93 (t, $J = 7.2$ Hz, 3H), 1.42−1.53 (m, 2H), 1.53−1.68 (m, 2H), 2.36 (s, 3H), 2.89 (t, $J = 7.4$ Hz, 2H), 7.06−7.26 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 13.6, 20.3, 22.0, 31.0, 32.5, 125.2, 126.2, 127.3, 129.9, 136.3, 137.2.

Supporting Information Available: Analytical data (^1H and ^{13}C NMR spectra) and literature citations for known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) $(PhS)_2$Ni(II)$(bpy)_2$ was prepared by the mixture of Ni(II)Cl_2(bpy) (4.2 mmol), bpy (8.8 mmol), and PhSNa (8.8 mmol) and was stirred in dioxane (10 mL) at 80 °C for 1.5 h. (a) Uchino, M.; Asagi, K.; Yamamoto, A.; Ikeda, S. *J. Organomet. Chem.* **1975**, *84*, 93−103.