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Transition-Metal-Free and Oxidant-Free Cross-Coupling of Arylhydrazines with Disulfides: Base-Promoted Synthesis of Unsymmetrical Aryl Sulfides

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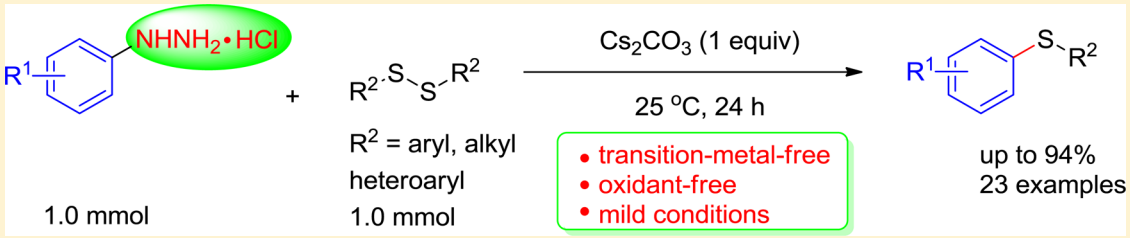
Supporting Information



ABSTRACT: A novel synthesis of unsymmetrical aryl sulfides, which requires no transition metal catalyst and no oxidant, was developed. This base-promoted cross-coupling reaction proceeded using arylhydrazines and 1 equiv amount of disulfides under inert gas conditions to afford the unsymmetrical aryl sulfides in good yields.

INTRODUCTION

Diaryl sulfides, which are used as pharmaceuticals, bioactive compounds, functional polymer materials,[1] and synthetic chemicals,[2] have received considerable attention. In particular, unsymmetrical aryl sulfides are of great importance as medicines for the treatment of various medical conditions such as cancer, Alzheimer's, Parkinson's, AIDS, neoplastic, HCV, diabetic, and parasitic diseases.[3] The importance of diaryl sulfides in biologically and pharmaceutically active compounds has sparked an increased interest toward improving methodologies to form these unsymmetrical compounds.

One of the most popular synthetic methods of unsymmetrical diaryl sulfides is the traditional Stadler−Ziegler reaction (Scheme 1),[4] where aryl amines are converted into the corresponding diazonium salts. These salts react with thiolates to yield unsymmetrical diaryl sulfides. The Stadler−Ziegler reaction has also been applied to the industrial manufacturing of diaryl sulfides.[5] Recently, a cross-coupling reaction of diazonium salts with thiols using a SET photoredox catalyst was reported.[6] In this reaction, diazonium salts and diazosulfides are formed as key intermediates, which are explosive and therefore their use is better avoided.[7]

Among the numerous synthetic methods for the aryl C−S bond formation, a powerful approach is the transition-metal-catalyzed C−S coupling reaction. Hitherto, many transition-metal-catalyzed systems including palladium,[8] nickel,[9] zinc,[10] copper,[11] iron,[12] rhodium,[13] silver,[14] and iridium[15] have been reported (Scheme 1). Although these reports were great breakthroughs for the synthesis of unsymmetrical sulfides, these transition-metal-catalyzed reactions usually need harsh conditions such as high temperatures[8−14] and microwave irradiation.[11f] Furthermore, high loadings of catalysts bearing specially designed ligands and/or strong bases are often required, because the strong coordination of thiolates to transition metal catalysts causes deactivation of the catalysts.[1b,16,17] Also, the tolerance of functional groups is limited due to the high temperatures and strong bases required in these reactions.

Moreover, to apply these reactions to industrial scale production, researchers often face the following problems: (1) Most of the transition metal catalysts, e.g., palladium catalysts, are very expensive, and some of them are toxic; and (2) The removal of transition metal residues from the target products is very costly. Therefore, the development of diaryl sulfide synthetic methods in the absence of transition metal catalysts is strongly desired from a practical perspective.

The formation of unsymmetrical aryl sulfides from diaryl disulfides, which are easy to handle, and aryl radicals generated from diazonium salts under reducing conditions is well-

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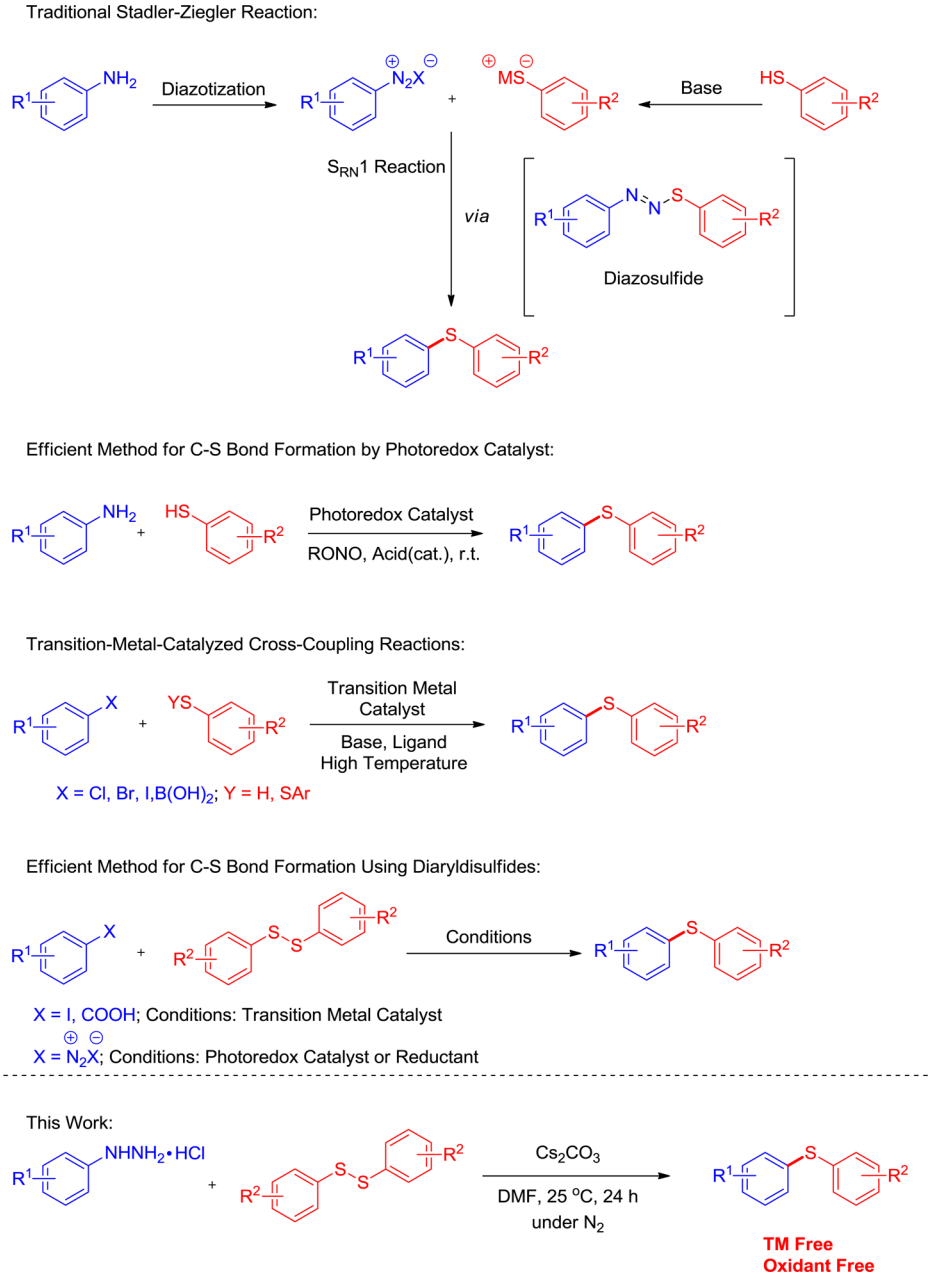
Scheme 1. Synthesis of Unsymmetrical Diaryl Sulfides



known.[14,18] Moreover, the generation of aryl radicals from arylhydrazines under oxidative conditions has been reported (homolytic aromatic substitution (HAS) reaction),[19] although, excess amounts of radical acceptors are generally required. Furthermore, diaryl disulfides are easily oxidized under air in the presence of a base and converted into benzenesulfonic acids.[20]

Herein, we report a transition-metal-free and oxidant-free cross-coupling reaction of arylhydrazines with diaryl disulfides overcoming the above difficulties. To the best of our knowledge, this is the first example of the synthesis of unsymmetrical diaryl sulfide using arylhydrazines and 1 equiv of diaryl disulfides under oxidant-free conditions.

RESULTS AND DISCUSSION

In the course of our previous studies on the cross-coupling of arylhydrazines with aminoheterocycles[21] and aromatic diamines,[22] we examined the cross-coupling reaction of 4-chlorophenylhydrazine hydrochloride (**1a**) with 4,4′-dinitrodiphenyl disulfide (**2a**) (Table 1). The coupling reaction of **1a** with 1 equiv of **2a** in the presence of potassium carbonate (2.0 equiv) in dimethyl sulfoxide (DMSO) occurred to afford 4-chlorophenyl 4′-nitrophenyl sulfide (**3aa**) in 75% yield (Table 1, entry 1).

A shorter reaction time slightly lowered the yield of **3aa** (Table 1, entry 1, footnote c). When the amounts of **2a** were decreased to 0.5 and 0.75 mmol, the yields of **3aa** were lowered (Table 1, entry 1, footnotes d and e). However, increasing the amounts of **2a** to 1.5 and 2.0 mmol, the similar yields of **3aa** were obtained (Table 1, entry 1, footnotes f and g). Another solvents (DMF, DMA, MeCN, and MeOH) gave **3aa** in reduced yields (Table 1, entries 2−5).

Using rubidium carbonate or cesium carbonate as base, **3aa** was formed in similar yields (Table 1, entries 6 and 7).

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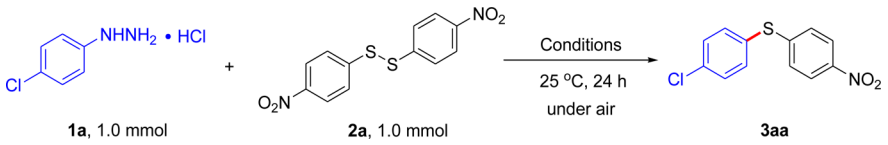
Table 1. Optimization of Synthesis of 3aa[a]

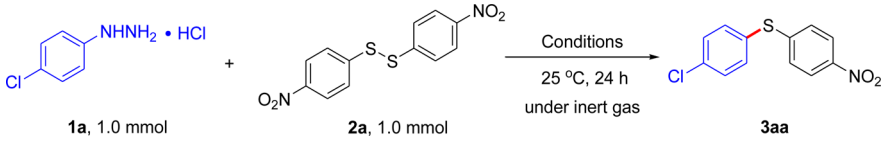


1a, 1.0 mmol **2a**, 1.0 mmol **3aa**

entry	solvent (mL)	base (equiv)	yield (%)[b]
1	DMSO (10)	K_2CO_3 (2.0)	75, 42[c], 44[d], 63[e], 77[f], 74[g]
2	DMF (10)	K_2CO_3 (2.0)	38
3	DMA (10)	K_2CO_3 (2.0)	39
4	MeCN (10)	K_2CO_3 (2.0)	9
5	MeOH (10)	K_2CO_3 (2.0)	17
6	DMSO (10)	Rb_2CO_3 (2.0)	74
7	DMSO (10)	Cs_2CO_3 (2.0)	73, 67[h], 61[i]
8	DMSO (10)	Li_2CO_3 (2.0)	11
9	DMSO (10)	Na_2CO_3 (2.0)	19
10	DMSO (10)	DBU (2.0)	54
11	DMSO (10)	DABCO (2.0)	16
12	DMSO (10)	Et_3N (2.0)	7
13	DMSO (10)	none	trace
14	DMSO (5)	K_2CO_3 (1.0)	69
15	DMSO (5)	Rb_2CO_3 (1.0)	42
16	DMSO (10)	Cs_2CO_3 (1.0)	72
17	DMSO (5)	Cs_2CO_3 (1.0)	79
18	DMSO (3)	Cs_2CO_3 (1.0)	82, 82[j]
19	DMSO (3)	Cs_2CO_3 (0.5)	5
20	DMSO (2)	Cs_2CO_3 (1.0)	81

[a]Reaction conditions: **1a** (1.0 mmol) and **2a** (1.0 mmol) at 25 °C for 24 h under air. [b]HPLC yields, calibration curve was shown in Figure S23. [c]Reaction time was 18 h. [d]**2a** (0.5 mmol). [e]**2a** (0.75 mmol). [f]**2a** (1.5 mmol). [g]**2a** (2.0 mmol). [h]Reaction temperature was 35 °C. [i]Reaction temperature was 80 °C for 1 h. [j]Isolated yield.

Table 2. Synthesis of 3aa under Inert Gas[a]



1a, 1.0 mmol **2a**, 1.0 mmol **3aa**

entry	solvent (mL)	base (equiv)	yield (%)[b]
1	DMSO (3)	Cs_2CO_3 (1.0)	41
2	DMSO (5)	Cs_2CO_3 (1.0)	54
3	DMSO (7.5)	Cs_2CO_3 (1.0)	59
4	DMSO (10)	Cs_2CO_3 (1.0)	64, 78[c], 70[d]
5	DMF (10)	Cs_2CO_3 (1.0)	70[c]
6	DMA (10)	Cs_2CO_3 (1.0)	65[d]
7	MeCN (10)	Cs_2CO_3 (1.0)	2[d]
8	MeOH (10)	Cs_2CO_3 (1.0)	Trace[d]

[a]Reaction conditions: **1a** (1.0 mmol) and **2a** (1.0 mmol) at 25 °C for 24 h under N_2. [b]HPLC yields. [c]Reaction time was 45 h. [d]Under argon atmosphere.

However, the use of lithium carbonate or sodium carbonate resulted in poor yields of **3aa** (Table 1, entries 8 and 9).

Higher reaction temperatures (35 and 80 °C for 1 h) in the presence of cesium carbonate as base gave slightly lowered the yields of **3aa** (Table 1, entry 7, footnotes h and i). When the reaction time was longer than 1 h at 80 °C, a complex mixture such as tar was formed.

As to organic bases, DBU was effective in this cross-coupling reaction and gave **3aa** in 54% yield (Table 1, entry 10). The use of DABCO or triethylamine was ineffective (Table 1, entries 11 and 12). In the absence of a base, **3aa** was not obtained (Table 1, entry 13).

The yields of **3aa** decreased when 1 equiv of K_2CO_3 or Rb_2CO_3 in 5 mL of DMSO were used (Table 1, entries 14 and 15). Instead, in the presence of 1 equiv of Cs_2CO_3, desired **3aa** was synthesized in good yield (Table 1, entry 17). The best result was obtained under high concentrated conditions (DMSO, 3 mL), and product **3aa** was generated in 82% yield (Table 1, entry 18). Using 0.5 equiv of base resulted in a remarkable decrease of yield of **3aa** (Table 1, entry 19). These results show that the base plays an important role in this cross-coupling reaction. Reducing the volume of solvent to 2 mL did not improve further the yield of **3aa** (Table 1, entry 20).

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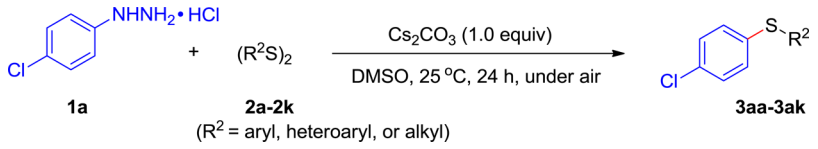
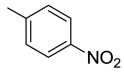
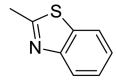
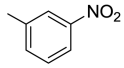
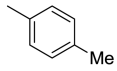
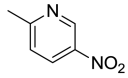
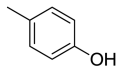
Table 3. Cross-Coupling Reaction of 1a with Disulfides 2[d]



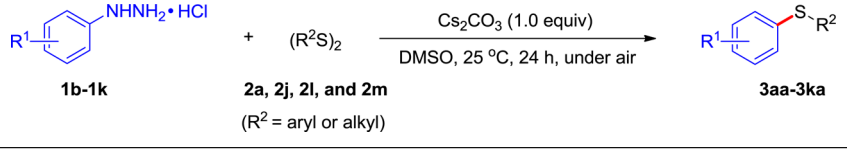
1a **2a-2k** **3aa-3ak**

(R^2 = aryl, heteroaryl, or alkyl)

R^2	yield (%)[a]	R^2	yield (%)[a]
	**3aa**, 82%, 70%[b]		**3af**, 76%
	**3ab**, 75%		**3ag**, 65%
	**3ac**, 40%		**3ah**, 20%
	**3ad**, 30%, 37%[b]		**3ai**, 93%
	**3ae**, 58%, 53%[c]		**3aj**, 81%
			**3ak**, 62%

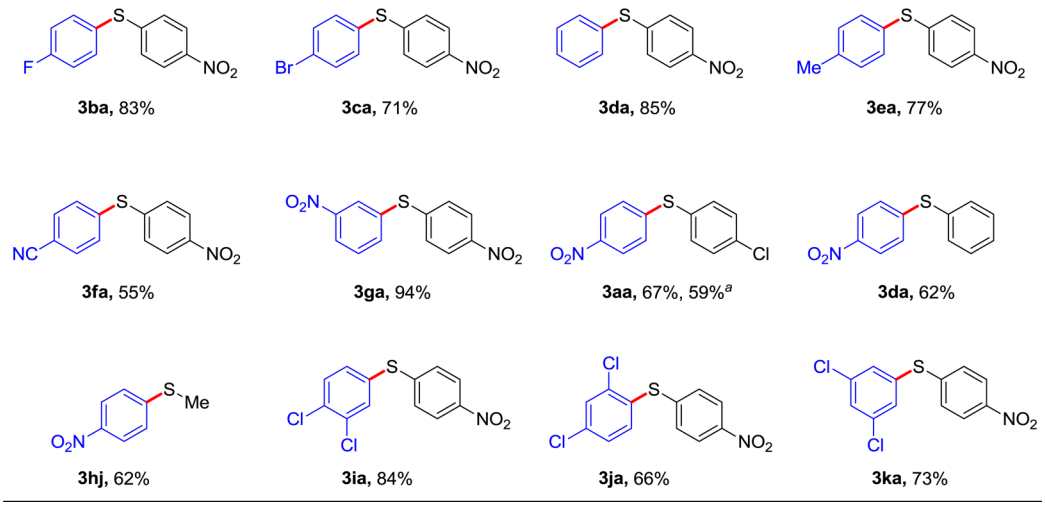
[a]Isolated yields. [b]Under argon atmosphere. [c]Cesium carbonate (3.0 mmol) was used. [d]Reaction conditions: **1a** (1.0 mmol) and **2** (1.0 mmol) at 25 °C for 24 h under air.

Table 4. Reaction of Arylhydrazines 1b−1k with Disulfides 2a, 2j, 2l, and 2m[b]



1b-1k **2a, 2j, 2l, and 2m** **3aa-3ka**

(R^2 = aryl or alkyl)



[a]Under argon atmosphere. [b]Reaction conditions: **1a** (1.0 mmol) and **2** (1.0 mmol) at 25 °C for 24 h under air. Isolated yields are shown.

Surprisingly, **3aa** was formed in 41% yield under an atmosphere of nitrogen (Table 2, entry 1). Under these conditions the yield was further increased when the amount of DMSO was increased to 5 mL, 7.5 mL, and 10 mL (Table 2, entries 2, 3, and 4), and improved to 78% when the reaction time was increased (45 h) (Table 2, entry 4, footnote c). A similar yield of **3aa** was observed under an argon atmosphere (Table 2, entry 4, footnote d) and the reaction also proceeded smoothly in DMF or DMA (*N*,*N*-dimethylacetamide) under nitrogen or argon atmospheres (Table 2, entries 5 and 6). These results strongly suggest that oxidants are not necessary for this cross-coupling reaction. However, **3aa** was hardly

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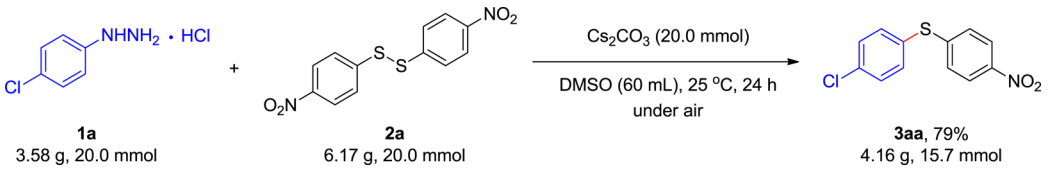
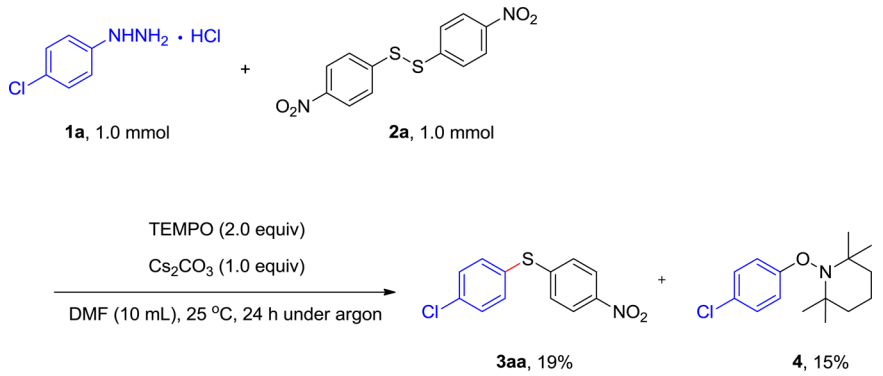
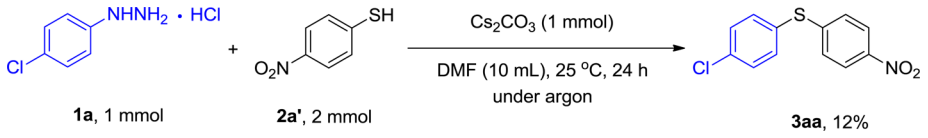
Scheme 2. Large-Scale Reaction



Scheme 3. Radical Trapping Experiment with TEMPO



Scheme 4. Reaction of 4-Nitrobenzenethiol with 1a



obtained when other solvents such as MeCN or MeOH were employed under an argon atmosphere (Table 2, entries 7 and 8). These low yields might be attributable to the very low solubility of **2a** in MeCN or MeOH.

With the optimized conditions in hand, the scope and limitations of the cross-coupling reaction of 4-chlorophenylhydrazine hydrochloride (**1a**) with a series of disulfides (**2a**–**2k**) were investigated (Table 3). The reaction of **1a** with 3,3′-dinitrodiphenyl disulfide (**2b**) provided compound **3ab** in 75% yield. In the case of 2,2′-dinitrodiphenyl disulfide (**2c**), the yield of **3ac** was lower probably due to steric effects. The reaction of **1a** with a diaryl disulfide bearing an electron-donating group such as methyl group provided **3ad** in 30% yield under air. A similar yield of **3ad** was also observed under an argon atmosphere.

The coupling reaction of **1a** with 4,4′-dihydroxydiphenyl disulfide (**2e**) having acidic protons using 1.0 equiv or 3.0 equiv of cesium carbonate was performed to afford the corresponding **3ae** in moderate yields. However, the coupling reaction of **1a** with 4,4′-diaminodiphenyl disulfide gave a complicated mixture.

Additionally, the cross-coupling with heteroaryl disulfides was successful. Thus, 2,2′-dibenzothiazolyl disulfide (**2f**) gave **3af** in high yield (76%) and with 4,4′-dipyridyl disulfide (**2g**) **3ag** was obtained in good yield. Instead, the use of 2,2′-dipyridyl disulfide (**2h**) resulted in a low yield (20%) of **3ah**. Interestingly, in the case of the 2,2′-dipyridyl disulfide derivative bearing a nitro group (**2i**), the coupling reaction provided **3ai** in excellent yield (93%). In addition, the coupling reactions with alkyl disulfides gave the corresponding unsymmetrical sulfides in good to high yields (**3aj** and **3ak**).

Next, the cross-coupling between a variety of arylhydrazine hydrochlorides (**1b**–**1k**) and several disulfides (**2a**, **2j**, **2l**, and **2m**) was examined, and the results are summarized in Table 4. The cross-coupling reaction of arylhydrazine hydrochlorides bearing either electron-withdrawing groups (i.e., fluoro, bromo, cyano, and nitro groups) or electron-donating groups (i.e., methyl group) with 4,4′-dinitrodiphenyl disulfide (**2a**) successfully afforded **3ba**–**3ga** in good to excellent yields (55–94%). However, the reaction of 4-methoxyphenylhydrazine hydrochloride having an electron-donating group with **2a** gave a complex mixture. Sulfide **3aa** was synthesized from 4-nitrophenylhydrazine hydrochloride (**1h**) and 4,4′-dichlorodiphenyl disulfide (**2l**) (67% under air and 59% under argon). Compound **1h** was allowed to react with diphenyl disulfide (**2m**) to afford **3da** in good yield (62%).

Using 4-nitrophenylhydrazine hydrochloride (**1h**) and dimethyl disulfide (**2j**), **3hj** was obtained in good yield (62%). Finally, the cross-coupling reaction could be applied to more hindered dichlorophenylhydrazine hydrochlorides (**1i**–**1k**) with 4,4′-dinitrodiphenyl disulfide (**2a**), giving the corresponding products (**3ia**–**3ka**) in good yields.

Even in a large-scale reaction (20 mmol), the cross-coupling of **1a** with **2a** proceeded smoothly to afford **3aa** in 79% yield (Scheme 2).

To clarify the mechanistic pathway for the cross-coupling reaction of arylhydrazines with disulfides, a radical trapping experiment was performed. Thus, using 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) under argon in DMF, the 4-chlorophenyl radical was trapped to afford **4** in 15% yield. Also, **3aa** was formed in a reduced yield (Scheme 3).

Next, the reaction of 4-chlorophenylhydrazine hydrochloride (**1a**) with 2 equiv of 4-nitrobenzenethiol (**2a′**) instead of 4,4′-nitrodiphenyl disulfide (**2a**) was investigated (Scheme 4). The desired product **3aa** was formed in a low yield (12%) under

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argon atmosphere. This result suggests that disulfide **2a** may formally act as an oxidant.

In summary, the generation of aryl radicals from arylhydrazines (HAS-type reaction) was successfully achieved in the absence of any oxidant. The base-promoted cross-coupling reaction of arylhydrazines with 1 equiv of disulfides under inert gas provides unsymmetrical aryl sulfides in good yields. This rare HAS-type reaction provides a practical synthesis of unsymmetrical aryl sulfides.

EXPERIMENTAL SECTION

General Information. All the starting materials were purchased from commercial sources and used without further purification. IR spectra were reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded on a 400 MHz spectrometer using $CDCl_3$ or DMSO-d_6 as solvent referenced to TMS (0 ppm) and $CHCl_3$ (7.26 ppm) or DMSO (2.50 ppm). ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ and DMSO-d_6 using $CDCl_3$ (77.0 ppm) and DMSO-d_6 (39.5 ppm) as standards. Chemical shifts are reported in parts per million (ppm). Coupling constants are in reported in hertz (*J*, Hz). The following abbreviations are used for the description of signals: s (singlet), d (doublet), t (triplet), q (quadruplet), and m (multiplet). Exact mass spectra were recorded using direct analysis in real time (DART-TOFMS). Analytical TLC was carried out on silica gel plates using short wave (254 nm) UV light. Silica gel (230−400 mesh) was used for column chromatography.

General Procedure for the Synthesis of Unsymmetrical Aryl Sulfide 3. A mixture of arylhydrazine hydrochlorides **1** (1.0 mmol), disulfides **2** (1.0 mmol), and cesium carbonate (326 mg, 1.0 mmol) in DMSO (3.0 mL) was stirred at 25 °C in air. The reactions were monitored by thin layer chromatography (TLC) and upon completion (24 h) quenched by the addition of water. Then, the reaction mixtures were extracted with ethyl acetate. The organic layer was washed with water and brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give crude products, which were purified by column chromatography (inner diameter: 3.0 cm and length: 30 cm) over silica gel (hexane/AcOEt) to afford pure products.

*4-Chlorophenyl 4′-nitrophenyl sulfide (**3aa**).* Compound **3aa** was synthesized from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3aa** (218 mg, 0.82 mmol, 82%) as a pale yellow block crystal; R_f = 0.44 (hexane/AcOEt = 95:5) (UV); mp 84.5−85.5 °C (Lit.[23] 83−84 °C); FT-IR (neat) 3091, 3059, 1502, 1331, 1078, 845 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.32 (d, *J* = 8.9 Hz, 2H), 7.59 (s, 4H), 8.14 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.4, 127.3, 129.0, 130.3, 134.8, 136.0, 145.3, 146.7; HRMS (DART-TOFMS) calcd for $C_{12}H_8ClNO_2S$ [M^+]: 264.9964, found 264.9944.

*4-Chlorophenyl 3′-nitrophenyl sulfide (**3ab**).* Compound **3ab** was prepared from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 3,3′-dinitrodiphenyl disulfide (**2b**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3ab** (198 mg, 0.75 mmol, 75%) as a pale yellow needle; R_f = 0.34 (hexane/AcOEt = 95:5) (UV); mp 70.5−71.5 °C (Lit.[24] 70−71 °C); FT-IR (neat) 3083, 3066, 1521, 1343, 727 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.50−7.55 (m, 4H), 7.64 (t, *J* = 8.2 Hz, 1H), 7.69 (td, *J* = 1.6 Hz, *J* = 8.2 Hz, 1H), 7.97 (t, *J* = 1.6 Hz, 1H), 8.10 (ddd, *J* = 1.6 Hz, *J* = 2.3 Hz, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 121.8, 123.0, 130.0, 130.9, 131.1, 133.8, 134.3, 135.3, 138.2, 148.4; HRMS (DART-TOFMS) calcd for $C_{12}H_8ClNO_2S$ [M^+]: 264.9964, found 264.9943.

*4-Chlorophenyl 2′-nitrophenyl sulfide (**3ac**).* Compound **3ac** was prepared according to the general procedure using 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 2,2′-dinitrodiphenyl disulfide (**2c**) (308 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3ac** (105 mg, 0.40 mmol, 40%) as a pale orange needle. R_f = 0.22 (hexane/AcOEt = 95:5) (UV); mp 96.0−97.0 °C (Lit.[25] 94−96 °C); FT-IR (neat) 3100, 1504, 1303, 1091 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.91 (dd, *J* = 1.4 Hz, *J* = 8.2 Hz, 1H), 7.42 (dt, *J* = 1.4 Hz, *J* = 8.2 Hz, 1H), 7.58−7.65 (m, 5H), 8.25 (dd, *J* = 1.4 Hz, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 125.8, 126.4, 128.5, 129.4, 130.4, 134.5, 135.3, 136.6, 137.0, 145.0; HRMS (DART-TOFMS) calcd for $C_{12}H_8ClNO_2S$ [M^+]: 264.9964, found 264.9947.

*4-Chlorophenyl 4′-tolyl sulfide (**3ad**).* The mixture of 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol), 4,4′-ditolyl disulfide (**2d**) (246 mg, 1.0 mmol), and cesium carbonate (1.0 equiv) in DMSO (3 mL) provided the desired **3ad** (71 mg, 0.30 mmol, 30% in air, and 86 mg, 0.37 mmol, 37% under argon). Recrystallization from hexane, gave **3ad** as a white solid; R_f = 0.40 (hexane) (UV); mp 71.5−72.5 °C (Lit.[24] 70−71 °C); FT-IR (neat) 2917, 1472, 1085, 804 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.31 (s, 3H), 7.20 (d, *J* = 8.7 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.7, 129.3, 129.4, 130.5, 130.5, 131.2, 132.5, 135.7, 138.2; HRMS (DART-TOFMS) calcd for $C_{13}H_{11}ClS$ [M^+]: 234.0270, found 234.0255.

*4-Chlorophenyl 4′-hydroxyphenyl sulfide (**3ae**).* Following the general procedure, compound **3ae** was synthesized from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 4,4′-dihydroxydiphenyl disulfide (**2e**) (250 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 2:1) afforded **3ae** (138 mg, 0.58 mmol, 58%) as an orange solid; Rf = 0.50 (hexane/AcOEt = 2:1) (UV); mp 66.0−67.5 °C (Lit.[26] 54−55 °C); FT-IR (neat) 3283, 1582, 1489, 1092, 810 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 6.85 (d, *J* = 8.7 Hz, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 9.95 (bs, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 116.9, 119.6, 128.4, 129.0, 130.1, 136.3, 138.0, 158.6; HRMS (DART-TOFMS) calcd for $C_{12}H_9ClOS$ [M^+]: 236.0063, found 236.0039.

*2-[(4′-Chlorophenyl)thio]benzothiazole (**3af**).* The desired product **3af** was synthesized from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 2,2′-dibenzothiazolyl disulfide (**2f**) (332 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 4:1) and recrystallization form hexane/AcOEt (9:1), gave **3af** (211 mg, 0.76 mmol, 76%) as a colorless plate crystal; R_f = 0.60 (hexane/AcOEt = 4:1) (UV); mp 59.0−60.0 °C (Lit.[27] 60−61 °C); FT-IR (neat) 3079, 3058, 1454, 1390, 747, 723 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.36 (dt, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H), 7.47 (dt, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 2H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.84−7.87 (m, 1H), 7.96 (dd, *J* = 1.2 Hz, *J* = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 121.5, 121.8, 124.7, 126.5, 127.9, 130.3, 134.9, 137.0, 153.3; HRMS (DART-TOFMS) calcd for $C_{13}H_9ClNS_2$ [$M + H^+$]: 277.9859, found 277.9839.

*4-[(4′-Chlorophenyl)thio]pyridine (**3ag**).* Compound **3ag** was obtained from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 4,4′-dipyridyl disulfide (**2g**) (220 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 2:3) gave **3ag** (144 mg, 0.65 mmol, 65%) as a brown solid; R_f = 0.40 (hexane/AcOEt = 2:3) (UV); mp 56.5−57.5 °C; FT-IR (neat) 3035, 1567, 1474, 1403, 1087, 822, 802 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.04 (dd, *J* = 1.6 Hz, *J* = 4.6 Hz, 2H), 7.59 (s, 4H), 8.38 (dd, *J* = 1.6 Hz, *J* = 4.6 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.8, 127.8, 130.2, 134.9, 136.5, 148.3, 149.7; HRMS (DART-TOFMS) calcd for $C_{11}H_9ClNS$ [$M + H^+$]: 222.0139, found 222.0126.

*2-[(4′-Chlorophenyl)thio]pyridine (**3ah**).* Following the general procedure, compound **3ah** was synthesized from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and 2,2′-dipyridyl disulfide (**2h**) (220 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 4:1) afforded **3ah** (44 mg, 0.20 mmol, 20%) as a brown oil; R_f = 0.50 (hexane/AcOEt = 4:1) (UV); FT-IR (neat) 3044, 2987, 1572, 1415, 1085, 755, 746 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.04 (td, *J* = 0.8 Hz, *J* = 8.0 Hz, 1H), 7.17 (ddd, *J* = 0.8 Hz, *J* = 4.4 Hz, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 2H),

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7.58 (d, J = 8.4 Hz, 2H), 7.67 (dt, J = 2.0 Hz, J = 8.0 Hz, 1H), 8.40 (ddd, J = 0.8 Hz, J = 2.0 Hz, J = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.8, 121.5, 129.3, 129.8, 134.1, 136.2, 137.5, 149.7, 158.9; HRMS (DART-TOFMS) calcd for $C_{11}H_9ClNS$ [M + H$^+$]: 222.0139, found 222.0120.

*2-[(4′-Chlorophenyl)thio]-5-nitropyridine (**3ai**).* The reaction of 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) with 2,2′-dithiobis(5-nitropyridine) (**2i**) (310 mg, 1.0 mmol) was performed according to the general procedure to afford compound **3ai**. Purification by column chromatography (hexane/AcOEt = 4:1) and recrystallization from hexane/AcOEt (9:1) gave **3ai** (249 mg, 0.93 mmol, 93%) as white needles; R_f = 0.50 (hexane/AcOEt = 4:1) (UV); mp 136.0−137.5 °C (Lit.[28] 136−138 °C); FT-IR (neat) 3053, 1568, 1508, 1343, 1089, 822, 747 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.21 (d, J = 9.0 Hz, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 8.40 (dd, J = 2.8 Hz, J = 9.0 Hz, 1H), 9.18 (d, J = 2.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 120.5, 127.0, 130.2, 132.3, 135.4, 137.1, 141.6, 145.0, 167.5; HRMS (DART-TOFMS) calcd for $C_{11}H_8ClN_2O_2S$ [M + H$^+$]: 266.9990, found 266.9968.

*1-Chloro-4-(methylthio)benzene (**3aj**).* Compound **3aj** was obtained from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and dimethyl disulfide (**2j**) (94 mg, 1.0 mmol) according to the general procedure. The crude product was purified by column chromatography using hexane and **3aj** (128 mg, 0.81 mmol, 81%) was obtained as a colorless oil; R_f = 0.30 (hexane) (UV); FT-IR (neat) 2984, 2919, 1474, 1093, 1010, 806 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s, 3H), 7.18 (d, J = 8.5 Hz, 2H), 7.25 (d, J = 8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.1, 127.9, 128.9, 130.9, 137.0; HRMS (DART-TOFMS) calcd for C_7H_7ClS [M$^+$]: 157.9957, found 157.9960.

*1-Chloro-4-(ethylthio)benzene (**3ak**).* Compound **3ak** was prepared from 4-chlorophenylhydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol) and diethyl disulfide (**2k**) (122 mg, 1.0 mmol) according to the general procedure. The resulting crude reaction mixture was purified by column chromatography using hexane to give the corresponding product **3ak** (107 mg, 0.62 mmol, 62%) as a colorless oil; R_f = 0.36 (hexane) (UV); FT-IR (neat) 2973, 2927, 2870, 1474, 1093, 1010, 809 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (t, J = 7.4 Hz, 3H), 2.92 (q, J = 7.4 Hz, 2H), 7.25 (s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 27.9, 128.9, 130.3, 131.7, 135.1; HRMS (DART-TOFMS) calcd for C_8H_9ClS [M$^+$]: 172.0113, found 172.0113.

*4-Fluorophenyl 4′-nitrophenyl sulfide (**3ba**).* According to the general procedure, compound **3ba** was synthesized from 4-fluorophenylhydrazine hydrochloride (**1b**) (163 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol). The crude mixture was purified by column chromatography (hexane/AcOEt = 95:5) and recrystallized from hexane to give **3ba** (206 mg, 0.83 mmol, 83%) as a pale yellow sticky crystal; R_f = 0.32 (hexane/AcOEt = 95:5) (UV); mp 97.4−98.4 °C (Lit.[29] 97−99 °C); FT-IR (neat) 3091, 1502, 1332, 1077, 831 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.26 (d, J = 9.0 Hz, 2H), 7.40 (dd, J_{HF} = 9.0 Hz, J = 9.0 Hz, 2H), 7.68 (dd, J_{HF} = 5.4 Hz, J = 9.0 Hz, 2H), 8.13 (d, J = 9.0 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 117.5 (d, J_{CF} = 22.9 Hz), 124.3, 125.1, 126.5, 137.4 (d, J_{CF} = 8.6 Hz), 145.0, 147.7, 163.1 (d, J_{CF} = 246.9 Hz); HRMS (DART-TOFMS) calcd for $C_{12}H_8FNO_2S$ [M$^+$]: 249.0260, found 249.0237.

*4-Bromophenyl 4′-nitrophenyl sulfide (**3ca**).* The reaction of 4-bromophenylhydrazine hydrochloride (**1c**) (224 mg, 1.0 mmol) with 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) was carried out according to the general procedure to provide the desired compound **3ca** (220 mg, 0.71 mmol, 71%) as a pale yellow block crystal after column chromatography (hexane) and recrystallization from hexane; R_f = 0.22 (hexane) (UV); mp 94.0−95.0 °C (Lit.[30] 94−96 °C); FT-IR (neat) 3092, 1504, 1334, 1008, 845, 742 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.33 (d, J = 9.2 Hz, 2H), 7.51 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 8.5 Hz, 2H), 8.14 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) d 123.4, 124.4, 127.4, 129.6, 133.2, 136.1, 145.3, 146.5; HRMS (DART-TOFMS) calcd for $C_{12}H_8BrNO_2S$ [M$^+$]: 308.9459, found 308.9447.

*4-Nitrophenyl phenyl sulfide (**3da**).* Compound **3da** was prepared from phenylhydrazine hydrochloride (**1d**) (145 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane) and recrystallization from hexane/AcOEt (9:1) gave **3da** (196 mg, 0.85 mmol, 85%) as a pale orange plate crystal; R_f = 0.18 (hexane) (UV); mp 55.0−56.0 °C (Lit.[23] 54−55 °C); FT-IR (neat) 3096, 3052, 1501, 1333, 741 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.27 (d, J = 8.9 Hz, 2H), 7.52−7.59 (m, 5H), 8.12 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.3, 126.8, 129.7, 129.9, 130.3, 134.4, 145.0, 147.5; HRMS (DART-TOFMS) calcd for $C_{12}H_{10}NO_2S$ [M+H$^+$]: 232.0427, found 232.0408.

*4-Nitrophenyl 4′-tolyl sulfide (**3ea**).* Compound **3ea** was synthesized from 4-tolylhydrazine hydrochloride (**1e**) (159 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane) and recrystallization from hexane/AcOEt (9:1) gave **3ea** (188 mg, 0.77 mmol, 77%) as pale yellow needles; R_f = 0.30 (hexane) (UV); mp 80.0−81.0 °C (Lit.[24] 78−79 °C); FT-IR (neat) 1508, 1338, 811, 738 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.23 (d, J = 9.2 Hz, 2H), 7.36 (d, J = 7.8 Hz, 2H), 7.49 (d, J = 7.8 Hz, 2H), 8.12 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 20.8, 124.3, 125.8, 126.2, 131.0, 134.9, 140.1, 144.8, 148.4; HRMS (DART-TOFMS) calcd for $C_{13}H_{11}NO_2S$ [M$^+$]: 245.0510, found 245.0507.

*4-Cyanophenyl 4′-nitrophenyl sulfide (**3fa**).* Following the general procedure, compound **3fa** was obtained from 4-cyanophenylhydrazine hydrochloride (**1f**) (170 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol). The crude mixture was purified by column chromatography with hexane/AcOEt = 4:1 to afford the desired compound **3fa** (140 mg, 0.55 mmol, 55%). Recrystallization from hexane/AcOEt (9:1) afforded **3fa** as pale yellow needles; R_f = 0.46 (hexane/AcOEt = 4:1) (UV); mp 153.5−154.5 °C (Lit.[31] 153−154 °C); FT-IR (neat) 3086, 2227, 1572, 1499, 1336, 825 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.55 (d, J = 9.2 Hz, 2H), 7.60 (d, J = 8.6 Hz, 2H), 7.90 (d, J = 8.6 Hz, 2H), 8.21 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 110.8, 118.3, 124.6, 130.5, 131.9, 133.5, 139.2, 142.9, 146.4; HRMS (DART-TOFMS) calcd for $C_{13}H_8N_2O_2S$ [M$^+$]: 256.0306, found 256.0288.

*3-Nitrophenyl 4′-nitrophenyl sulfide (**3ga**).*[18a] Compound **3ga** was obtained from 3-nitrophenylhydrazine hydrochloride (**1g**) (190 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 7:1) afforded the desired product **3ga** (258 mg, 0.94 mmol, 94%) as a yellow powder; R_f = 0.23 (hexane/AcOEt = 7:1) (UV); mp 122.0−123.0 °C (decomp.); FT-IR (neat) 3088, 1540, 1512, 1337, 1315, 850, 841, 738 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.84 (t, J = 7.9 Hz, 1H), 8.06 (d, J = 9.2 Hz, 2H), 8.11 (ddd, J = 0.8 Hz, J = 2.0 Hz, J = 7.9 Hz, 1H), 8.31 (t, J = 2.0 Hz, 1H), 8.34−8.38 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 115.8, 124.4, 125.2, 128.1, 128.5, 131.2, 142.1, 147.2, 148.6, 151.3; HRMS (DART-TOFMS, neg) calcd for $C_{12}H_7N_2O_4S$ [M − H$^+$]: 275.0132, found 275.0149.

*4-(Methylthio)nitrobenzene (**3hj**).* Following the general procedure, compound **3hj** was synthesized from 4-nitrophenylhydrazine hydrochloride (**1h**) (190 mg, 1.0 mmol) and dimethyl disulfide (**2j**) (94 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 9:1) and recrystallization from hexane gave **3hj** (105 mg, 0.62 mmol, 62%) as a pale brown plate crystal; R_f = 0.30 (hexane/AcOEt = 9:1) (UV); mp 69.4−70.4 °C (Lit.[32] 65−67 °C); FT-IR (neat) 3092, 3001, 2915, 1583, 1505, 1330, 1092, 829, 737 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.59 (s, 3H), 7.47 (d, J = 8.7 Hz, 2H), 8.14 (d, J = 8.7 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.0, 123.8, 125.3, 144.1, 149.0; HRMS (DART-TOFMS) calcd for $C_7H_7NO_2S$ [M$^+$]: 169.0197, found 169.0195.

*3,4-Dichlorophenyl 4′-nitrophenyl sulfide (**3ia**).* Compound **3ia** was obtained from 3,4-dichlorophenylhydrazine hydrochloride (**1i**) (214 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. The crude product was purified by column chromatography (hexane/AcOEt = 95:5) and

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recrystallized from hexane/AcOEt (9:1) to give **3ia** (251 mg, 0.84 mmol, 84%) as white needles; R_f = 0.22 (hexane/AcOEt = 95:5) (UV); mp 110.0−111.0 °C; FT-IR (neat) 3088, 3058, 1579, 1500, 1336, 1079, 1032, 839, 812, 739 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.41 (d, J = 8.9 Hz, 2H), 7.53 (dd, J = 2.3 Hz, J = 8.2 Hz, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.87 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) d 124.5, 128.2, 131.5, 132.1, 132.5, 132.6, 133.8, 135.0, 145.4, 145.6; HRMS (DART-TOFMS) calcd for $C_{12}H_7Cl_2NO_2S$ [M^+]: 298.9575, found 298.9550.

*2,4-Dichlorophenyl 4′-nitrophenyl sulfide (**3ja**).* Compound **3ja** was synthesized from 2,4-dichlorophenylhydrazine hydrochloride (**1j**) (214 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol) according to the general procedure. Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3ja** (198 mg, 0.66 mmol, 66%) as a pale brown block crystal; R_f = 0.20 (hexane/AcOEt = 95:5) (UV); mp 76.0−77.0 °C; FT-IR (neat) 3095, 1575, 1506, 1336, 1084, 1033, 846, 810, 742 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.35 (d, J = 8.9 Hz, 2H), 7.56 (dd, J = 2.3 Hz, J = 8.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 1H), 7.90 (d, J = 2.3 Hz, 1H), 8.16 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.5, 127.9, 128.5, 128.9, 130.3, 135.6, 137.2, 138.0, 144.3, 145.7; HRMS (DART-TOFMS) calcd for $C_{12}H_7Cl_2NO_2S$ [M^+]: 298.9575, found 298.9549.

*3,5-Dichlorophenyl 4′-nitrophenyl sulfide (**3ka**).* Following the general procedure, the product **3ka** was synthesized from 3,5-dichlorophenylhydrazine hydrochloride (**1k**) (214 mg, 1.0 mmol) and 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol). Purification by column chromatography (hexane/AcOEt = 95:5) and recrystallization from hexane/AcOEt (9:1) gave **3ka** (218 mg, 0.73 mmol, 73%) as a white block crystal; R_f = 0.19 (hexane/AcOEt = 95:5) (UV); mp 93.5−94.5 °C; FT-IR (neat) 3071, 1556, 1506, 1330, 1082, 840, 797, 666 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 7.48 (d, J = 9.2 Hz, 2H), 7.60 (d, J = 1.8 Hz, 2H), 7.74 (t, J = 1.8 Hz, 1H), 8.19 (d, J = 9.2 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 124.5, 128.9, 129.1, 131.1, 135.2, 144.3, 146.0; HRMS (DART-TOFMS) calcd for $C_{12}H_7Cl_2NO_2S$ [M^+]: 298.9575, found 298.9548.

Large-Scale Synthesis of 3aa. Compound **3aa** was prepared from a mixture of 4-chlorophenylhydrazine hydrochloride (**1a**) (3.58 g, 20.0 mmol), 4,4′-dinitrodiphenyl disulfide (**2a**) (6.17 g, 20.0 mmol), and cesium carbonate (6.52 g, 20.0 mmol) in DMSO (60 mL) under air, according to the general procedure. The reaction was monitored by thin layer chromatography (TLC) and completed after 24 h. Purification by column chromatography (inner diameter: 5 cm and length: 30 cm) over silica gel (hexane/AcOEt = 95:5) gave product **3aa** (4.16 g, 79%) in a pure form.

Radical-Trapping Experiment with TEMPO. To a mixture of 4-chlorophenyl- hydrazine hydrochloride (**1a**) (179 mg, 1.0 mmol), 4,4′-dinitrodiphenyl disulfide (**2a**) (308 mg, 1.0 mmol), and cesium carbonate (326 mg, 1.0 mmol) in DMF (10 mL), TEMPO (313 mg, 2.0 mmol) was added. The solution was stirred at room temperature under an argon atmosphere for 24 h. The resulting solution was quenched by the addition of water and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a crude product. Purification by column chromatography over silica gel afforded **3aa** (19%) and 4-chloro-1-(2′,2′,6′,6′-tetramethylpiperidinyloxy)benzene (**4**) (40 mg, 15%). Compound **4** was recrystallized from hexane to give a colorless plate crystal; R_f = 0.62 (hexane); mp 89.5−90.5 °C (Lit.[21] 89.5−90.5 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 0.99 (s, 6H), 1.21 (s, 6H), 1.38−1.44 (m, 1H), 1.53−1.68 (m, 5H), 7.11 (d, J = 9.4 Hz, 2H), 7.15 (d, J = 9.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.0, 20.4, 32.5, 39.7, 60.4, 115.2, 124.3, 128.5, 162.2.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00767.

^1H NMR, ^{13}C NMR spectra, and calibration curve for **3aa** (PDF)

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Notes

The authors declare no competing financial interest.

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