Efficient Copper-Catalyzed S-Arylation of Thiols with Aryl Bromides and Chlorides

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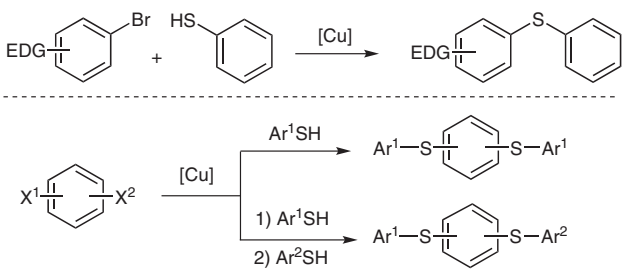
Abstract: An efficient copper-catalyzed system for C–S cross-coupling of aromatic thiols with aryl bromides and chlorides has been developed using 1,2,3,4-tetrahydroquinoline-8-ol as a ligand. It is noteworthy that this method is proved to be especially effective for aryl bromides with electron-donating groups. By this protocol, a variety of thioethers as well as symmetrical and unsymmetrical bis-thioethers are obtained in excellent yields with an exceptional level of functional group tolerance and high chemoselectivity.

Key words: copper catalyst, aryl bromides, aryl chlorides, cross-coupling, organic sulfides

The C–S bonds proverbially exist in compounds with biological and pharmaceutical impact and in molecules of useful polymeric materials.[1] For example, various aryl sulfides are used for the treatment of cancer[2] and human immunodeficiency virus diseases.[3] The development of efficient S-arylation methods has been a subject of interest in synthetic chemistry since Migita first reported the palladium-catalyzed cross-coupling of aryl halides with thiols.[4] A wide range of transition metals was used to catalyze this coupling reaction, including palladium,[5] nickel,[6] cobalt[7], copper,[8] and indium.[9] Among them, the development of copper-catalyzed methods is attractive due to the relatively low cost and environmentally negative influence of the process.

During the last decade copper-catalyzed cross-coupling reactions of aryl iodides with thiols have enabled the synthesis of aryl sulfides in good yields under mild reaction conditions.[10] However, only a few reports employed cheaper and more widely available aryl bromides and chlorides as arylating agents.[10a–f,11] Furthermore, most of the systems reported in the limited literature were not evidently effective for the aryl bromides with electron-donating groups. Therefore, it remains a tremendous challenge to develop an efficient copper-catalyzed method for the S-arylation with inactivated aryl bromides and aryl chlorides.

In our previous copper-catalyzed S-arylation with aryl iodides, when *p*-bromoiodobenzene was used as a substrate, both coupling reactions of C–I and C–Br bonds with thiols were observed.[12] This encouraged us to extend the method to inactivated aryl bromides and even to aryl chlorides. Furthermore, as shown in Scheme 1, we would be able to achieve several symmetrical bis-thioethers in one-pot fashion and even obtain unsymmetrical bis-thioethers based on the activity difference of C–X bonds.



Scheme 1 Pathways of experimental design

To optimize the reaction conditions, the coupling reaction of thiophenol and bromobenzene was used as a model reaction. When the reaction temperature was raised to 130 °C and the time was prolonged to 48 hours with DMF as solvent, a significant increase was observed (Table 1, entry 5). Utilizing the slightly stronger base Cs_2CO_3 proved to be critical for the reaction (Table 1, entry 7). Yield was further improved by increasing the amount of catalyst loading to 20 mol%. Thus, the optimal reaction conditions were obtained as shown in entry 8.

Firstly, with the optimized conditions, the aryl bromides with electron-donating groups, such as methyl and amino, gave the prospective diaryl thioethers in excellent yields (Table 2, **2a**, **2b**, and **2c**). In the case of 4-bromoanisole with methoxy group, unexpectedly, the GC yield of phenylsulfanylanisole was only 53% (Table 2, **2d**). Other by-products, anisole, phenol, methyl phenyl thioether, and 4-methoxyphenyl phenyl ether were detected by GC-MS. Some side-reactions, such as dehalogenation of 4-bromoanisole, reaction of anisole and thiophenol resulting in phenol and methyl phenyl thioether as reported,[13] and reaction of phenol with 4-bromoanisole subsequently to form 4-methoxyphenyl phenyl ether, were observed (side-reaction process is described in detail in the Supporting Information). Heterocyclic bromides such as 2-bromopyridene also could be employed in this coupling reaction with good to excellent yield (Table 2, **2e**). Further, this catalytic system is highly efficient for aryl chlorides with electron-withdrawing groups as well, such as cyano, acetyl, and trifluoromethyl groups (Table 2, **2g**, **2i**, **2h**, **2l**, **2m** and **2n**). Secondly, the sterically hindered *ortho*-sub-

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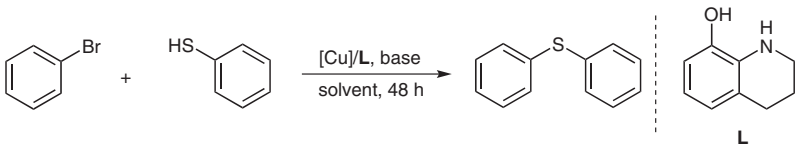
Table 1 Optimization of the Reaction Conditions[a]

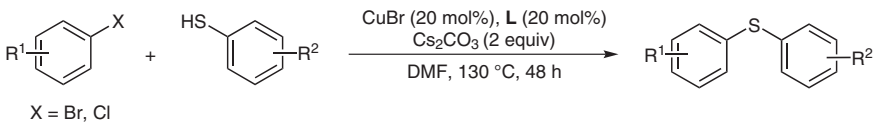


Entry	Solvent	[Cu]	Base	[Cu] (mol%)	Temp (°C)	Yield (%)
1	DMSO	CuBr	K_2CO_3	20	120	28
2	DMSO	CuI	K_2CO_3	20	120	18
3	DMSO	CuCl	K_2CO_3	20	120	28
4	DMF	CuBr	K_2CO_3	20	120	31
5	DMF	CuBr	K_2CO_3	10	130	61
6	DMF	CuBr	K_3PO_4	10	130	48
7	DMF	CuBr	Cs_2CO_3	10	130	88
8	DMF	CuBr	Cs_2CO_3	20	130	97

[a] Reaction conditions: bromobenzene (0.75 mmol), thiophenol (0.5 mmol), [Cu] (10 or 20 mol%), **L** (0.1 mmol), base (1.0 mmol), and solvent (1.5 mL) stirred for 48 h under argon. Yield (GC) was calibrated with diphenyl ether as an internal standard.

stituted aryl bromides and chlorides gave the corresponding products in satisfactory yields (Table 2, **2f** and **2g**). Thirdly, this copper-catalyzed system indicates a high chemoselectivity. On the one hand, on the basis of difference in the activity of C–Br and C–Cl bonds of 4-bromochlorobenzene, we were able to selectively obtain 4-chlorophenyl phenyl thioether in good yield by controlling the reaction temperature (Table 2, **2j**). On the other hand, the Ar–Br or Ar–Cl coupled with SH selectively without any reaction with NH_2 present at the aryl ring of the thiol (Table 2, **2k** and **2l**).

Table 2 The C–S Coupling Reaction of Aryl Halides and Aromatic Thiols[a]



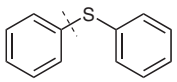
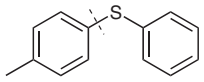
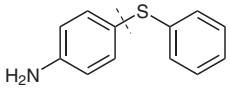
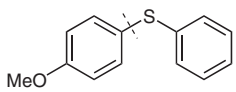
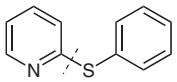
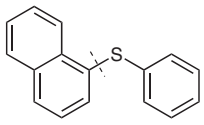
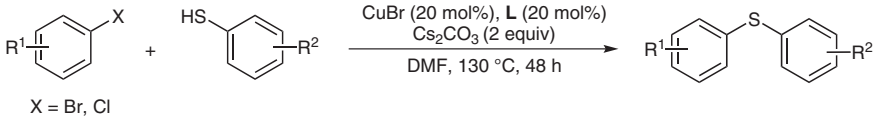
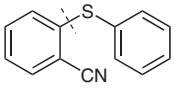
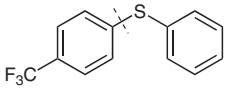
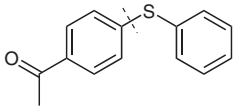
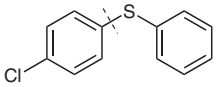
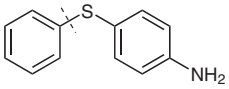
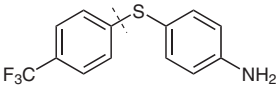
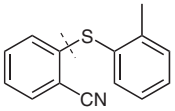
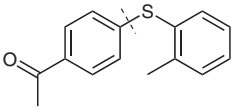
X			Yield (%)[b]
Br	**2a**		91
Br	**2b**		99
Br	**2c**		81
Br	**2d**		53[c]
Br	**2e**		97
Br	**2f**		75

Table 2 The C–S Coupling Reaction of Aryl Halides and Aromatic Thiols[a] (continued)



X			Yield (%)[b]
Cl	**2g**		72
Cl	**2h**		82
Cl	**2i**		86
Br	**2j**		77[d]
Br	**2k**		83
Cl	**2l**		68
Cl	**2m**		57
Cl	**2n**		81

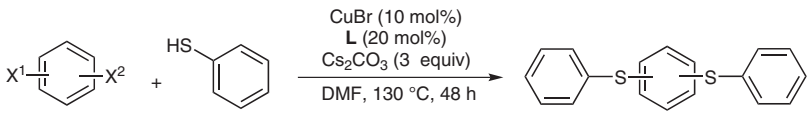
[a] Reaction conditions: aryl halides (0.75 mmol), thiols (0.5 mmol), CuBr (20 mol%), **L** (20 mol%), Cs_2CO_3 (1 mmol), and DMF (1.5 mL) stirred at 130 °C for 48 h under argon.
[b] Isolated yield.
[c] GC yield.
[d] At 100 °C.

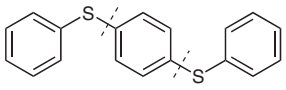
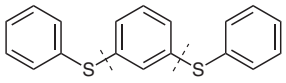
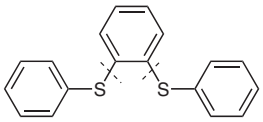
It was interesting to note that several symmetrical and unsymmetrical bis-thioethers could be prepared using this catalytic system. So far, there are only a few scattered literature reports concerning the fact that both halogen groups in aryl dihalides could simultaneously take part in the C–S coupling reaction in a one-pot fashion.[10f,14,15a] The optimized reaction conditions for symmetrical bis-thioethers were somewhat different from those of mono-thioethers. The amount of CuBr was reduced to 10 mol%, the quantity of Cs_2CO_3 was increased to 3 equivalents, and the molar ratio of thiophenol to aryl dihalides was 2.2:1. Whether the substrate was *para*-, *meta*-, or *ortho*-aryl dihalides, the symmetrical bis-thioethers were all obtained in excellent yields (Table 3, **3a**, **3b**, and **3c**). Because the aryl chlorides are less reactive, the reaction of *p*- or *o*-dichlorobenzene afforded the corresponding bis-thioethers in moderate to good yields.

Encouraged by the success of symmetrical bis-thioethers achieved, the synthesis of unsymmetrical bis-thioethers from 4-bromoiodobenzene was attempted based on the difference in the activity between C–I and C–Br bonds. As shown in Scheme 2, first, 4-bromophenyl phenyl thioether was prepared first in satisfactory yield by regulating the temperature (Scheme 2). Then, 4-bromophenyl phenyl thioether reacted with other aromatic thiols. Ultimately, several unsymmetrical bis-thioethers were obtained in good to excellent yields (Scheme 2, **4a**–**c**). In the case of *p*-chlorothiophenol, yield is slightly lower due to the weak nucleophilicity of *p*-chlorothiophenol and the debromination side-reaction of 4-bromophenyl phenyl thioether.

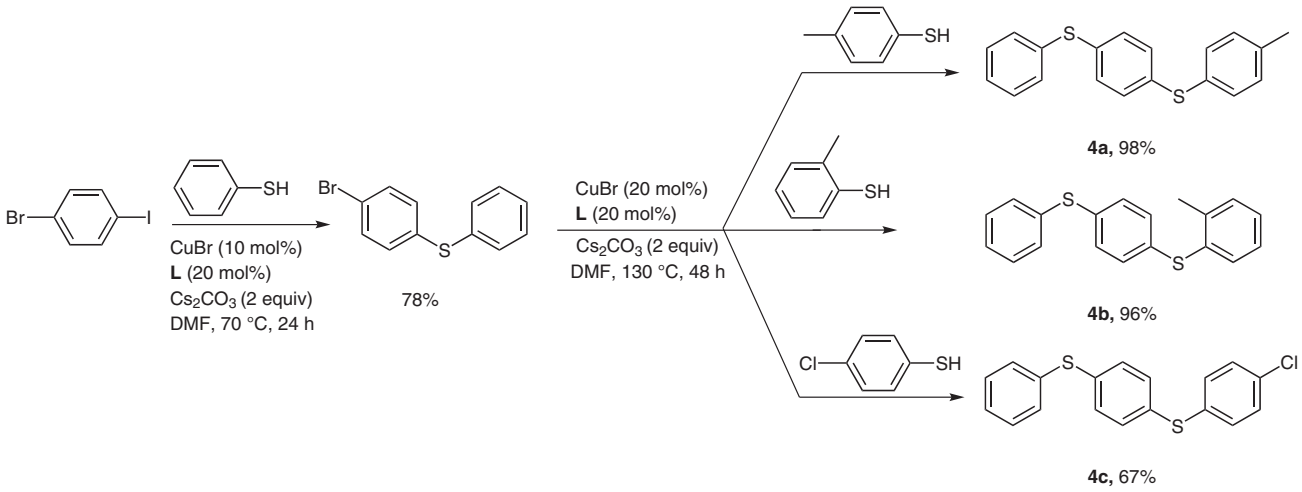
Thus, this reaction offered an easy access to a library of symmetrical and unsymmetrical bis-thioethers. Besides, it is found to be much potential in synthesizing PPS oligomers, which have a long history as commercial thermo-

Table 3 The C–S Coupling Reaction of Aryl Dihalides and Thiophenol[a]



Product		X^1	X^2	Yield (%)[b]
3a		Br	I	92
		Br	Br	97
		Cl	I	95
		Cl	Br	99
		Cl	Cl	78
3b		Br	I	99
3c		Br	I	93
		Br	Br	99
		Cl	Cl	70[c]

[a] Reaction conditions: aryl dihalides (0.5 mmol), thiophenol (1.1 mmol), CuBr (10 mol%), **L** (20 mol%), Cs_2CO_3 (1.5 mmol), and DMF (1.5 mL) stirred at 130 °C for 48 h under argon.
[b] Isolated yield.
[c] GC yield; 30% 2-chlorophenyl phenyl thioether was also formed. *o*-Dichlorobenzene was completely consumed.



Scheme 2 Synthesis of unsymmetrical bis-thioethers

plastics and classic sulfur-based polymers because these polymers exhibit excellent mechanical properties, high stability, conductivity, energy storage ability, fire retardant, high refractive index, etc.[15]

In conclusion, we have developed a highly efficient copper-catalyzed cross-coupling reaction of both aryl bromides and chlorides with aryl thiols. Furthermore, we successfully achieved symmetrical and unsymmetrical bis-thioethers in good to excellent yields. In addition, this catalytic system showed wide functional group tolerance and well chemoselectivity. We believe that this method exhibits the potential in organic synthesis on account of the low cost and availability of aryl bromides and chlorides.

^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent on a Varian INOVA 400 NMR spectrometer (^1H 400 MHz, ^{13}C 100 MHz) with respect to internal TMS. GC-MS was obtained on HP 6890GC/5973MSD spectrometer. MS were recorded on HP1100 HPLC/MS spectrometer. HRMS analyses were performed on UPLC/Q-Tof Micro spectrometer. Petroleum ether (PE) used refers to the fraction boiling in the range 60–90 °C. The 1,2,3,4-tetrahydro-quinoline-8-ol (**L**) was prepared as reported in the literature.[16]

Diphenyl Thioether (2a);[17] Typical Procedure

A flame-dried test tube with a magnetic stirring bar was charged with CuBr (14 mg, 0.1 mmol), ligand (15 mg, 0.1 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), thiophenol (55 mg, 0.5 mmol), bromobenzene (118 mg, 0.75 mmol), and DMF (1.5 mL) under argon. The mixture was stirred at 130 °C for 48 h, then cooled to r.t. and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum.

The residue was purified by column chromatography on silica gel with PE as eluent; colorless oil (Table 2). CAS: 139-66-2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.21 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.6, 130.9, 129.1, 126.9.

GC-MS (EI): *m*/*z* = 186 $[M]^+$.

4-Tolyl Phenyl Thioether (2b)[17]
The crude product was purified over a silica gel column using PE; colorless oil. CAS: 3699-01-2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 8.0 Hz, 2 H), 7.25–7.14 (m, 5 H), 7.09 (d, *J* = 8.0 Hz, 2 H) 2.30 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.6, 137.3, 132.3, 131.5, 130.1, 129.9, 129.1, 126.5, 21.2.

GC-MS (EI): *m*/*z* = 200 $[M]^+$.

4-Aminophenyl Phenyl Thioether (2c)[7,18]
Following the typical procedure, **2c** was prepared from 4-bromoaniline and thiophenol. The crude product was purified over a silica gel column using EtOAc–PE (1:3); pale solid; mp 95.7–96.2 °C (Lit.[18] mp 96–96.5 °C). CAS: 1135-14-4.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.4 Hz, 2 H), 7.21 (t, *J* = 7.6 Hz, 2 H), 7.13–7.08 (m, 3 H), 6.69 (d, *J* = 8.4 Hz, 2 H), 3.98 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 139.7, 136.1, 128.9, 127.6, 125.4, 121.1, 116.1.

GC-MS (EI): *m*/*z* = 201 $[M]^+$.

2-(Phenylthio)pyridine (2e)[7]
The crude product was purified over a silica gel column using EtOAc–PE (2:25); colorless oil. CAS: 3111-54-4.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 4.4 Hz, 1 H), 7.60–7.57 (m, 2 H), 7.46–7.39 (m, 4 H), 6.99–6.96 (t, *J* = 6.2 Hz, 1 H), 6.87 (d, *J* = 8.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.6, 149.6, 136.8, 135.0, 131.0, 129.7, 129.2, 121.3, 119.9.

GC-MS (EI): *m*/*z* = 186 $[M]^+$.

MS (API): *m*/*z* = 188 $[M + H]^+$.

1-Naphthyl Phenyl Thioether (2f)[5c]
The crude product was purified over a silica gel column using PE; colorless oil. CAS: 7570-98-1.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.39–8.36 (m, 1 H), 7.87–7.83 (m, 2 H), 7.65 (d, *J* = 7.2 Hz, 1 H), 7.52–7.48 (m, 2 H), 7.41 (t, *J* = 7.2 Hz, 1 H), 7.22–7.13 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.1, 134.4, 133.8, 132.7, 131.4, 129.4, 129.2, 129.1, 128.7, 127.1, 126.6, 126.3, 126.0, 125.8.

GC-MS (EI): *m*/*z* = 236 $[M]^+$.

2-(Phenylthio)benzonitrile (2g)[19a,b]
The crude product was purified over a silica gel column using EtOAc–PE (3:20); slightly yellow solid; mp 56.1–57.1 °C (Lit.[19b] mp 56.5–58 °C). CAS: 91804-55-6.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.0 Hz, 1 H), 7.49–7.47 (m, 2 H), 7.43–7.38 (m, 4 H), 7.28–7.24 (m, 1 H), 7.13 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.4, 133.7, 133.6, 133.0, 132.0, 130.0, 129.8, 129.0, 126.5, 117.0, 113.0.

GC-MS (EI): *m*/*z* = 211 $[M]^+$.

Phenyl 4-(Trifluoromethyl)phenyl Sulfide (2h)[19a]
The crude product was purified over a silica gel column using PE; colorless oil. CAS: 53451-90-4.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.47 (m, 4 H), 7.41–7.38 (m, 3 H), 7.27–7.25 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 133.7 (2 C), 132.6, 129.9 (2 C), 128.8, 128.4 (2 C), 128.3 (q, $^2J_{C,F}$ = 32.6 Hz), 125.9 (d, $^3J_{C,F}$ = 3.5 Hz), 124.2 (q, $^1J_{C,F}$ = 271.6 Hz).

GC-MS (EI): *m*/*z* = 254 $[M]^+$.

1-[4-(Phenylthio)phenyl]ethanone (2i)[5c,20]
The crude product was purified over a silica gel column using EtOAc–PE (1:40); white solid; mp 64–64.8 °C (Lit.[20] mp 64–66 °C). CAS: 10169-55-8.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, *J* = 8.4 Hz, 1 H), 7.51–7.48 (m, 2 H), 7.41–7.39 (m, 3 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 2.55 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.3, 145.1, 134.6, 134.0, 132.2, 129.8, 129.0, 128.9, 127.5, 26.6.

GC-MS (EI): *m*/*z* = 228 $[M]^+$.

4-Chlorophenyl Phenyl Thioether (2j)[8d]
The crude product was purified over a silica gel column using PE; colorless oil. CAS: 13343-26-5.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.3, 134.8, 133.2, 132.2, 131.5, 129.49, 129.48, 127.6.

GC-MS (EI): *m*/*z* = 220 $[M]^+$, 222 $[M + 2]^+$.

4-Aminophenyl Phenyl Thioether (2k ≡ 2c)
Following the typical procedure, 4-aminophenyl phenyl thioether was also prepared by reacting bromobenzene with 4-aminothiophenol. The crude product was purified over a silica gel column using EtOAc–PE (1:3). For analytical and spectral data, see under **2c**.

4-[4-(Trifluoromethyl)phenylthio]aniline (2l)[21]
The crude product was purified over a silica gel column using EtOAc–PE (1:6); slightly yellow solid; mp 89.6–90.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 (d, *J* = 8.4 Hz, 2 H), 7.33 (d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 8.4 Hz, 2 H), 6.72 (d, *J* = 8.4 Hz, 2 H), 3.98 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 145.9, 137.1, 126.1, 125.7, 118.4, 116.3.

GC-MS (EI): *m*/*z* = 269 $[M]^+$.

2-(*o*-Tolylthio)benzonitrile (2m)[22]
The crude product was purified over a silica gel column using EtOAc–PE (1:80); slightly yellow solid; mp 65–65.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.63 (d, *J* = 7.6 Hz, 1 H), 7.47 (d, *J* = 7.6 Hz, 1 H), 7.38–7.34 (m, 3 H), 7.25–7.18 (m, 2 H), 6.84 (d, *J* = 8.0 Hz, 1 H), 2.39 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 142.2, 135.7, 133.8, 133.1, 131.3, 130.2, 130.0, 128.1, 127.4, 125.8, 117.1, 111.7, 20.9.

GC-MS (EI): *m*/*z* = 225 $[M]^+$.

1-[4-(*o*-Tolylthio)phenyl]ethanone (2n)
The crude product was purified over a silica gel column using EtOAc–PE (1:20); slightly yellow solid; mp 57.7–59 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.8 Hz, 2 H), 7.52 (d, *J* = 8.0 Hz, 1 H), 7.35–7.34 (m, 2 H), 7.25 (m, 1 H), 7.08 (d, *J* = 8.4 Hz, 2 H), 2.54 (s, 3 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 197.2, 145.1, 142.4, 136.0, 134.3, 131.3, 130.5, 129.9, 129.1, 127.3, 126.5, 26.6, 20.8.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14}OS$ + Na: 265.0663; found: 265.0656.

4-Bromophenyl Phenyl Thioether[23]

This compound was prepared as shown in Scheme 2 employing the molar ratios of the starting materials used for the preparation of **3a** (see below). The crude product was purified over a silica gel column using PE; colorless oil. CAS: 65662-88-6.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.4 Hz, 2 H), 7.36–7.24 (m, 5 H), 7.16 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.7, 135.0, 132.4, 132.2, 131.7, 129.5, 127.7, 121.0.

GC-MS (EI): *m*/*z* = 264 [M]$^+$, 266 [M + 2]$^+$.

1,4-Bis(phenylthio)benzene (3a);[15a,24] Typical Procedure

A flame-dried test tube with a magnetic stirring bar was charged with CuBr (7 mg, 0.05 mmol), ligand (15 mg, 0.1 mmol), Cs_2CO_3 (489 mg, 1.5 mmol), thiophenol (121 mg, 1.1 mmol), *p*-dibromobenzene (118 mg, 0.5 mmol), and DMF (1.5 mL) under argon. The mixture was stirred at 130 °C for 48 h, then cooled to r.t. and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography on silica gel with PE as eluent (Table 3).

White solid; mp 81.6–82.1 °C (Lit.[15a] mp 81.3 °C). CAS: 3459-94-7.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35 (d, *J* = 7.2 Hz, 4 H), 7.32–7.28 (t, *J* = 7.2 Hz, 4 H), 7.27–7.23 (t, *J* = 7.2 Hz, 2 H), 7.21 (s, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.2, 135.1, 131.6, 131.3, 129.5, 127.6.

GC-MS (EI): *m*/*z* = 294 [M]$^+$.

1,3-Bis(phenylthio)benzene (3b)[24]

Colorless oil. CAS: 2974-10-9.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 7.4 Hz, 4 H), 7.28–7.20 (m, 7 H), 7.18–7.10 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 134.6, 132.0, 131.4, 129.8, 129.4, 128.5, 127.7.

GC-MS (EI): *m*/*z* = 294 [M]$^+$.

1,2-Bis(phenylthio)benzene (3c)[24]

Colorless oil. CAS: 3379-36-0.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.21 (m, 10 H), 7.14–7.08 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5, 134.6, 131.9, 131.5, 129.5, 129.2, 127.6.

GC-MS (EI): *m*/*z* = 294 [M]$^+$.

1-Phenylsulfanyl-4-*p*-tolylsulfanylbenzene (4a); Typical Procedure

Following the typical experimental procedure given above for **3a**, 4-bromophenyl phenyl thioether was synthesized first from 4-bromoiodobenzene and thiophenol as shown in Scheme 2; then the residue was purified by column chromatography on silica gel eluting with PE. After that, a flame-dried test tube with a magnetic stirring bar was charged with CuBr (14 mg, 0.1 mmol), ligand (15 mg, 0.1 mmol), Cs_2CO_3 (326 mg, 1.0 mmol), 4-methylthiophenol (62 mg, 0.5 mmol), 4-bromophenyl phenyl thioether (198 mg, 0.75 mmol), and DMF (1.5 mL) under argon. The mixture was stirred at 130 °C for 48 h, then cooled to r.t. and the resulting mixture was extracted with EtOAc (3 × 25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under vacuum. The residue was purified by column chromatography on silica gel with PE as eluent to give **4a**; white solid; mp 59–60 °C (Lit.[25] mp 55.5 °C). CAS: 96802-31-2.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 7 H), 7.21 (d, *J* = 8.0 Hz, 2 H), 7.16–7.14 (m, 4 H), 2.35 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2, 136.7, 135.7, 133.9, 132.9, 131.7, 131.2, 130.6, 130.4, 130.1, 129.4, 127.3, 21.3.

GC-MS (EI): *m*/*z* = 308 [M]$^+$.

1-Phenylsulfanyl-4-*o*-tolylsulfanylbenzene (4b)

The crude product was purified over a silica gel column using PE as eluent; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 5 H), 7.24–7.20 (m, 5 H), 7.15 (d, *J* = 8.0 Hz, 1 H), 7.08 (d, *J* = 8.0 Hz, 2 H), 2.37 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.0, 135.7, 135.6, 133.8, 133.6, 133.1, 131.7, 131.2, 130.9, 129.9, 129.4, 128.5, 127.3, 127.0, 20.8.

GC-MS (EI): *m*/*z* = 308 [M]$^+$.

(4-Chlorophenyl)[4-(phenylthio)phenyl]sulfane (4c)[26]

The crude product was purified over a silica gel column using PE as eluent; white solid; mp 92.3–92.8 °C (Lit.[26] mp 92–93 °C). CAS: 60420-81-7.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.0 Hz, 2 H), 7.32–7.26 (m, 3 H), 7.24–7.20 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 134.7, 134.2, 134.0, 133.5, 132.4, 131.9, 131.7, 131.0, 129.6, 129.5, 127.8.

GC-MS (EI): *m*/*z* = 328 [M]$^+$, 330 [M + 2]$^+$.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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