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Transition-Metal-Free Acid-Mediated Synthesis of Aryl Sulfides from Thiols and Thioethers

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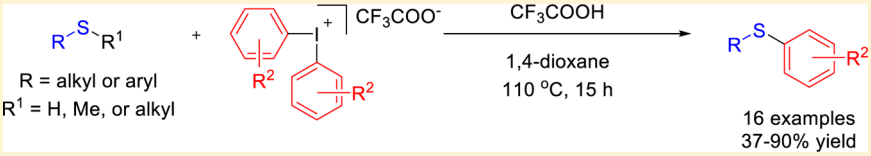
Supporting Information



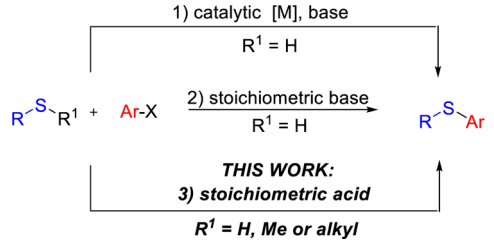
ABSTRACT: The preparation of diaryl and alkyl aryl sulfides via acid-mediated coupling of thiols and thioethers with diaryliodonium salts is reported. The scope, limitations, and mechanism of the transformation are discussed.

The preparation of aryl sulfides constitutes an active and important area of synthetic organic chemistry because of the extensive biological applications of compounds containing C_{aryl}–S bonds.[1,2] For instance, aryl sulfides and aryl sulfoxides are key components of commercial pharmaceuticals, including Lansoprazole, Sulindac, Esomeprazole, and Quetiapine. Aryl sulfides are also present in molecules that are used to treat cancer, inflammation, asthma, Alzheimer's disease, Parkinson's disease, and HIV.[3−8] Finally, aryl sulfides can serve as precursors to photoacid generators (PAGs), which are widely used in paints, anticorrosives, microelectronics, and coatings.[9,10]

One of the most common routes to aryl sulfides involves the transition-metal-catalyzed cross-coupling of aryl halides or pseudo-halides with thiols under basic conditions.[11−16] A number of base-mediated, transition-metal-free reactions for aryl sulfide synthesis have also been reported.[17−25] While these represent highly useful transformations, the vast majority of current synthetic methods for aryl sulfide synthesis require at least one of the following: (1) the use of strongly basic media, (2) the use of transition-metal catalysts and/or mediators, (3) the use of an inert atmosphere, and/or (4) the use of a thiol substrate. These requirements represent disadvantages with respect to functional group tolerance, ease of product purification (particularly for biological applications), and flexibility of synthetic strategies.

We report herein an orthogonal, metal-free method for the synthesis of aryl sulfides that involves the reaction of either RSH or RSR′ with diaryliodonium salts (Scheme 1), versatile reagents that have found diverse applications.[26] These reactions proceed under acidic conditions, thereby offering the potential for complementary substrate scope and functional group tolerance relative to base and/or transition-metal-catalyzed transformations. This new method offers additional advantages of compatibility with ambient air and moisture as well as the flexibility to use either thiols or thioethers as starting materials. This report describes the optimization, scope, and mechanistic investigations of this transformation.

Scheme 1. Strategies for Aryl Sulfide Formation



Initial investigations focused on the reaction of 1 equiv of thioanisole (PhSMe) with 1 equiv of diphenyliodonium trifluoroacetate (Ph_2ITFA) to generate diphenyl sulfide (Ph_2S). We were pleased to find that with trifluoroacetic acid (TFA) as the solvent, this reaction provided a 26% yield of the desired product after 24 h at 100 °C (Table 1, entry 1). We next examined the reaction in a variety of alternative solvents using 5 equiv of TFA as an additive. As shown in entries 2−5 of Table 1, these studies revealed that 1,4-dioxane was the optimal cosolvent. In dioxane, the reaction proceeded efficiently in the presence of 5 equiv of either TFA (entry 5) or NaTFA (entry 6). However, overall the yields were more reproducible using TFA. Notably, replacing TFA with NaOAc or HOAc resulted in reduced yields (entries 7 and 8). Further optimization of the phenylation reaction showed that the best yields were obtained with 8 equiv of TFA for 15 h at 110 °C to provide Ph_2S in 77% yield (entry 9). Finally, because copper catalysts have been used in similar reactions,[21] several Cu(I) and Cu(II) salts were tested under our optimal conditions. As shown in entry 10, the addition of 0.1 equiv of copper had a minimal impact on the overall reaction yield. The reaction time for this transformation could be reduced from 15 to 1.5 h by using a microwave reactor (entry 11).

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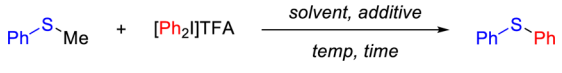
Table 1. Optimization of Thioanisole Phenylation[a]



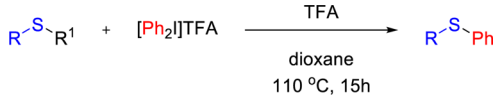
entry	solvent	additive (equiv)	yield[e] (%)
1	TFA	none	26
2	toluene	TFA (5)	36
3	acetic acid	TFA (5)	49
4	DMF	TFA (5)	59
5	1,4-dioxane	TFA (5)	65
6	1,4-dioxane	NaTFA (5)	55
7	1,4-dioxane	NaOAc (5)	3
8	1,4-dioxane	AcOH (5)	13
9	1,4-dioxane	TFA (8)[b]	77
10	1,4-dioxane	TFA (8), [Cu] (0.1)[c]	65–78
11[d]	1,4-dioxane	TFA (8)	83

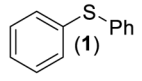
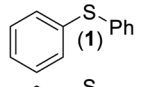
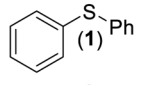
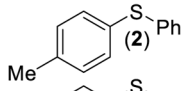
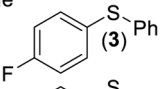
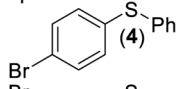
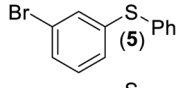
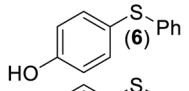
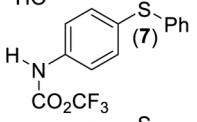
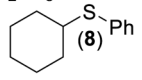
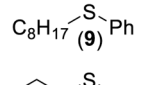
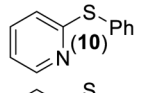
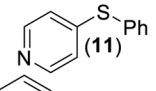
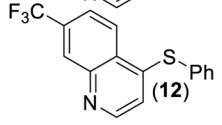
[a]One equivalent (0.093 mmol) of Ph_2ITFA, 1 equiv (0.093 mmol) of thioanisole, 5 equiv (0.47 mmol) of additive, 0.31 M in solvent at 100 °C for 24 h. [b]Eight equivalents (0.74 mmol) of TFA at 110 °C for 15 h. [c][Cu] = $Cu(OAc)_2$, $Cu(OTf)_2$, Cu(II) acetylacetonate, $CuCl_2$, CuCN, or CuCl. [d]MW conditions: 1.5 h, 120 °C, 140 W. [e]Yields determined by GC using hexadecane as the internal standard.

As shown in Table 2, a variety of thiols and thioanisole derivatives are effective substrates for this transformation. With alkyl aryl sulfides, the C_{sp3}–S bond is cleaved exclusively, resulting in diarylsulfide products (entries 2 and 3). Thioanisoles bearing both electron rich and electron deficient aryl groups showed good reactivity (entries 4–7). Bromide, OH, and NH_2 substituents were tolerated on the thioanisole moiety. Importantly, in the latter two cases, no N- or O-arylation products were detected. However, the aniline functionality underwent trifluoroacetylation under the reaction conditions. Primary and secondary alkyl thiols are also viable substrates, providing alkyl aryl sulfide products in moderate yields (entries 10 and 11). In contrast, when unsymmetrical primary dialkyl sulfides [$C_{sp3(primary)}$–S–$C_{sp3(primary)}$] were used as starting materials, mixtures of the two possible alkyl aryl products were obtained. In the case of mixed secondary and primary dialkyl sulfides [$C_{sp3(primary)}$–S–$C_{sp3(secondary)}$], there was a preference for formation of the secondary alkyl aryl sulfide product. However, again these transformations provided lower yields.[27] Finally, pyridine and quinoline-containing thiols could also be converted to the analogous heterocyclic thioethers using this method (entries 12–14). These types of nitrogen heterocycles are often incompatible with transition-metal-catalyzed C–S coupling reactions because of their strong coordinating abilities.

The scope of this transformation was next assessed using a series of different hypervalent iodine coupling partners. A series of different Ar_2ITFA reagents were prepared from the corresponding aryl iodide and aryl boronic acid, using a synthesis described by Olofsson and co-workers[28] followed by anion exchange.[29] As summarized in Table 3, diaryliodonium salts bearing both electron-withdrawing and -donating groups participate in the arylation of thioanisole (entries 2–6). This reaction also tolerates bromine-substituted diaryliodonium salts (entries 6–8). For example, bis(4-bromophenyl) sulfide **15**, which represents a useful precursor to photoacid generators, was obtained in high yield through the coupling of 4-bromothioanisole with bis(4-bromophenyl)iodonium trifluoroacetate (entry 7). Finally, this reaction proceeds well using diaryliodonium salts with *meta* substitution (entry 8). In contrast, reactions with *ortho*-substituted diaryliodonium salts provided significantly lower yields (entry 9).

Table 2. Scope of Sulfides and Thioethers[a]



entry	R	R^1	product	yield[b](%)
1	Ph	H	 (1)	83
2	Ph	Me	 (1)	77
3	Ph	Bu	 (1)	79
4	4-MeC_6H_4	Me	 (2)	82
5	4-FC_6H_4	Me	 (3)	77
6	4-BrC_6H_4	Me	 (4)	57
7	3-BrC_6H_4	Me	 (5)	54
8	4-HOC_6H_4	Me	 (6)	90
9	4-$H_2NC_6H_4$	Me	 (7)	38
10	Cy	H	 (8)	56
11	Oct	H	 (9)	64
12	2-C_5H_4N	H	 (10)	56
13	4-C_5H_4N	H	 (11)	49
14	7-$CF_3C_9H_5N$	H	 (12)	69

[a]One equivalent (0.5 mmol) of Ph_2ITFA, 1 equiv (0.5 mmol) of thiol or thioether, 8 equiv (4.0 mmol) of TFA, 0.31 M in 1,4-dioxane at 110 °C for 15 h. [b]Isolated yields. All results are an average of two runs.

We propose that this reaction proceeds via the mechanism proposed in Scheme 2. This sequence involves (1) initial oxidation of the thioether or thiol with Ar_2ITFA to generate sulfonium salt **A** or **B** followed by (2) nucleophilic substitution with trifluoroacetate to liberate the aryl sulfide product and alkyl ester **C**. Importantly, there is precedent in the literature that supports the viability of both of these steps. For example, it has been shown that diaryliodonium salts can react with substituted sulfides to produce sulfonium salts, albeit in the presence of a copper catalyst.[21,30] Furthermore, Takeuchi and co-workers have hypothesized that in a related reaction, a

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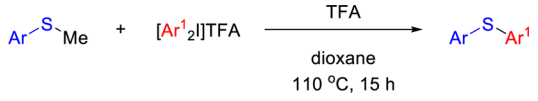
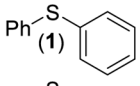
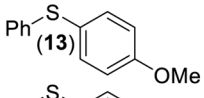
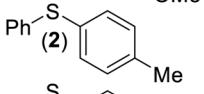
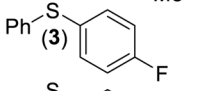
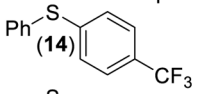
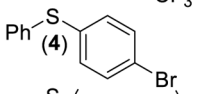
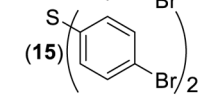
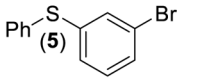
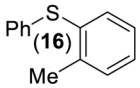
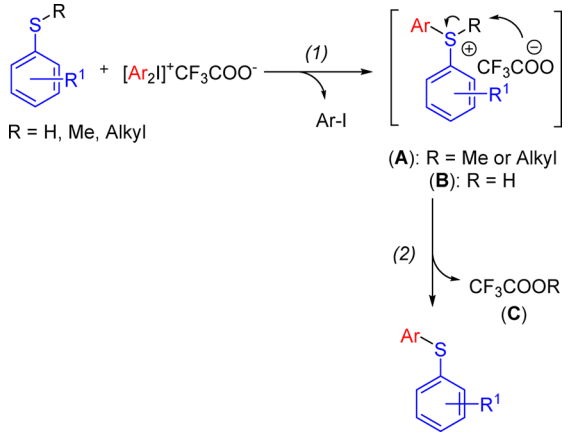
Table 3. Scope of Diaryliodonium Salts[a]



entry	Ar	Ar^1	product	yield[b](%)
1	Ph	Ph		77
2	Ph	4-$MeOC_6H_4$		37
3	Ph	4-MeC_6H_4		85
4	Ph	4-FC_6H_4		78
5	Ph	4-$CF_3C_6H_4$		57
6	Ph	4-BrC_6H_4		70
7	4-BrC_6H_4	4-BrC_6H_4		58
8	Ph	3-BrC_6H_4		55
9	Ph	2-MeC_6H_4		17[c]

[a]One equivalent (0.5 mmol) of Ar^1_2ITFA, 1 equiv (0.5 mmol) of thioether, 8 equiv (4.0 mmol) of TFA, 0.31 M in 1,4-dioxane at 110 °C for 15 h. [b]Isolated yields. [c]GC yield. All results are an average of two runs.

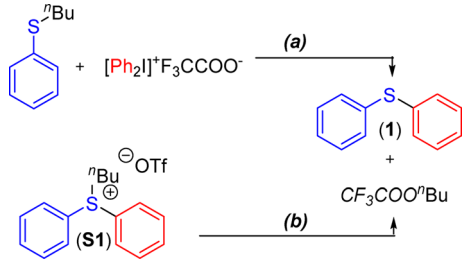
Scheme 2. Proposed Mechanism for Thioether Arylation



putative aminosulfonium salt intermediate can undergo nucleophilic substitution with the conjugate base of a strong acid.[31]

To test our mechanistic hypothesis, we prepared *n*-butyl phenyl sulfide[32] and, after subjecting it to our reaction conditions, observed *n*-butyl trifluoroacetate and diphenyl sulfide by GC–MS (Scheme 3a). Under these reaction conditions, the putative sulfonium intermediate **S1** (analogous to **A**, where R^1 = H, Ar = Ph, and R = butyl, in Scheme 2) was not detected *in situ* by HRMS, thus suggesting that it is short-lived and that oxidation of the sulfide with Ar_2ITFA is likely rate-limiting. We also generated the sulfonium salt butyl diphenyl sulfonium triflate **S1** (Ph_2SBuOTf)[21] independently and subjected it to our reaction conditions. This sulfonium salt underwent rapid conversion to **1** and F_3CCOO-^{n}Bu (in ≤30 min) under our reaction conditions (Scheme 3b).[33,34] These observations further support our mechanistic proposal.[35]

Scheme 3. Reaction Mechanism Probes



In conclusion, this paper demonstrates the arylation of thiols and thioethers using diaryliodonium salts under acidic conditions and provides evidence of a mechanism that proceeds through a sulfonium salt intermediate. This reaction represents a versatile and robust route to aryl thioether products and is complementary to existing procedures.

EXPERIMENTAL SECTION

General. All reactions were conducted on the benchtop without precautions to exclude air or moisture. All reagents were purchased and used without further purification. Sulfonium salt S1 was synthesized using the method described in ref 21. Symmetric iodonium salts were synthesized using the methods described in refs 28 and 29.

General Procedure for Arylation. To a 20 mL scintillation vial containing Ar_2ITFA (1 equiv, 0.5 mmol) were added a thiol or thioether (1 equiv, 0.5 mmol) and 1,4-dioxane (1.6 mL, 0.31 M). After the contents had been mixed, trifluoroacetic acid (8 equiv, 4 mmol) was added. The vial was sealed with a Teflon-lined cap, and the reaction mixture was placed into one of the wells of an aluminum block preheated to 110 °C. After being stirred for 15 h, the reaction mixture was cooled to room temperature, and water (10 mL) was added. The solution was extracted with diethyl ether (3 × 5 mL), and the combined organic layers were washed with water (5 mL). The organic layer was then dried over sodium sulfate and concentrated *in vacuo*. The crude reaction mixture was purified by (1) flash column chromatography on silica using hexanes or a hexanes/ethyl acetate mixture or (2) vacuum short path distillation followed by passage through a silica plug with ether. Yields reported in Tables 1–3 represent an average of two runs.

Diphenyl Sulfide (1). The crude product was purified by distillation (bp = 296 °C at 760 Torr). Brown oil. From thiophenol and Ph_2ITFA (Table 2, entry 1; 77 mg, 83% yield); from thioanisole and Ph_2ITFA (Table 2, entry 2, and Table 3, entry 1; 72 mg, 77% yield); from butyl phenyl sulfide and Ph_2ITFA (Table 2, entry 3; 74 mg, 79% yield). HRMS EI [M^+] calcd for $C_{12}H_{10}S$, 186.0503; found, 186.0500. ^{1}H and ^{13}C NMR data matched those reported in the literature.[36]

Phenyl p-Tolyl Sulfide (2). The crude product was purified by distillation (bp = 308 °C at 760 Torr). Brown oil. From methyl *p*-tolyl sulfide and Ph_2ITFA (Table 2, entry 4; 82 mg, 82% yield); from thioanisole and (4-$MeC_6H_4)_2$ITFA (Table 3, entry 3; 85 mg, 85% yield). HRMS EI [M^+] calcd for $C_{13}H_{12}S$, 200.0600; found, 200.0605. ^{1}H and ^{13}C NMR data matched those reported in the literature.[36]

4-Fluorophenyl Phenyl Sulfide (3). The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.48 in hexanes). Colorless oil. From 4-fluorothioanisole

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and Ph_2ITFA (Table 2, entry 5; 79 mg, 77% yield); from thioanisole and $(4\text{-}FC_6H_4)_2$ITFA (Table 3, entry 4; 80 mg, 78% yield). ^{19}F NMR (471 MHz, $CDCl_3$): δ −113.1. HRMS EI [M^+] calcd for $C_{12}H_9FS$, 204.0409; found, 204.0405. ^{1}H and ^{13}C NMR data matched those reported in the literature.[36]

*4-Bromophenyl Phenyl Sulfide (**4**).* The crude product was purified by distillation (bp = 355 °C at 760 Torr). Brown oil. From 4-bromothioanisole and Ph_2ITFA (Table 2, entry 6; 76 mg, 57% yield); from thioanisole and $(4\text{-}BrC_6H_4)_2$ITFA (Table 3, entry 6; 94 mg, 70% yield). HRMS EI [M^+] calcd for $C_{12}H_9BrS$, 263.9608; found, 263.9611. ^{1}H and ^{13}C NMR data matched those reported in the literature.[36]

*3-Bromophenyl Phenyl Sulfide (**5**).* The crude product was purified by distillation (bp = 352 °C at 760 Torr). Brown oil. From 3-bromothioanisole and Ph_2ITFA (Table 2, entry 7; 71 mg, 54% yield); from thioanisole and $(3\text{-}BrC_6H_4)_2$ITFA (Table 3, entry 8; 73 mg, 55% yield). HRMS EI [M^+] calcd for $C_{12}H_9BrS$, 263.9608; found, 263.9611. ^{1}H and ^{13}C NMR data matched those reported in the literature.[37]

*4-Hydroxyphenyl Phenyl Sulfide (**6**).* The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.55 in a 25% EtOAc/75% hexanes mixture). Brown oil (91 mg, 90% yield). HRMS EI [M^+] calcd for $C_{12}H_{10}OS$, 202.0452; found, 202.0449. ^{1}H and ^{13}C NMR data matched those reported in the literature.[38]

*2,2,2-Trifluoro-N-[4-(phenylthio)phenyl]acetamide (**7**).* The crude product was purified by flash column chromatography (R_f = 0.23 in a 10% EtOAc/90% hexanes mixture). Colorless oil (57 mg, 38% yield). ^{1}H NMR (700 MHz, $CDCl_3$): δ 9.51 (1H, br s), 7.50−7.51 (m, 2H), 7.25−7.35 (multiple peaks, 7H). ^{13}C NMR (175 MHz, $CDCl_3$): δ 154.7 (q, J_{C-F} = 37 Hz), 135.0, 134.2, 133.9, 131.6 (q, J_{C-F} = 26 Hz), 129.3, 127.6, 127.5, 121.1, 115.6 (q, J_{C-F} = 290 Hz). ^{19}F NMR (471 MHz, $CDCl_3$): δ −75.7. HRMS electrospray (m/z): [M + H] calcd for $C_{14}H_{11}F_3NOS$, 298.0508; found, 298.0503.

*Cyclohexyl Phenyl Sulfide (**8**).* The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.52 in hexanes). Colorless oil (54 mg, 56% yield). HRMS EI [M^+] calcd for $C_{12}H_{16}S$, 192.0973; found, 192.0971. ^{1}H and ^{13}C NMR data matched those reported in the literature.[36]

*Octyl Phenyl Sulfide (**9**).* The crude product was purified by flash column chromatography (R_f = 0.43 in hexanes). Colorless oil (71 mg, 64% yield). HRMS EI [M^+] calcd for $C_{14}H_{22}S$, 222.1442; found, 222.1439. ^{1}H and ^{13}C NMR data matched those reported in the literature.[24]

*Phenyl 2-Pyridyl Sulfide (**10**).* Before extraction with diethyl ether, 2 M NaOH was added until the solution was basic. The crude product was purified by distillation (bp = 321 °C at 760 Torr). Brown oil (52 mg, 56% yield). HRMS electrospray (m/z): [M + H] calcd for $C_{11}H_{10}NS$, 188.0528; found, 188.0527. ^{1}H and ^{13}C NMR data matched those reported in the literature.[24]

*Phenyl 4-Pyridyl Sulfide (**11**).* Before extraction with diethyl ether, 2 M NaOH was added until the solution was basic. The crude product was purified by column chromatography on an Isolera Flash Purification System (R_f = 0.52 in a 50% EtOAc/50% hexanes mixture). Colorless oil (46 mg, 49% yield). HRMS electrospray (m/z): [M + H] calcd for $C_{11}H_{10}NS$, 188.0528; found, 188.0524. ^{1}H and ^{13}C NMR data matched those reported in the literature.[39]

*3-(Phenylthio)-7-(trifluoromethyl)quinoline (**12**).* Before extraction with diethyl ether, 2 M NaOH was added until the solution was basic. The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.33 in a 25% EtOAc/75% hexanes mixture). Yellowish solid (103 mg, 69% yield, mp = 61−63 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.64 (d, J = 6.3 Hz, 1H), 8.38 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 7.76 (m, 1H), 7.60 (m, 2H), 7.50−7.52 (multiple peaks, 3H), 6.83 (d, J = 6.3 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6, 149.2, 146.6, 135.3, 131.4 (q, J_{C-F} = 33 Hz), 130.1, 130.0, 128.6, 127.7 (q, J_{C-F} = 4 Hz), 127.3, 124.8, 123.7 (q, J_{C-F} = 273 Hz), 121.90 (q, J_{C-F} = 3 Hz), 119.0. ^{19}F NMR (377 MHz, $CDCl_3$): δ −62.74. HRMS EI [M^+] calcd for $C_{16}H_{10}F_3NS$, 305.0486; found, 305.0485.

*4-Methoxyphenyl Phenyl Sulfide (**13**).* The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.50 in a 10% EtOAc/90% hexanes mixture). Colorless oil (40 mg, 37% yield). HRMS EI [M^+] calcd for $C_{13}H_{12}OS$, 216.0609; found, 216.0607. ^{1}H and ^{13}C NMR data matched those reported in the literature.[36]

*Phenyl 4-Trifluoromethylphenyl Sulfide (**14**).* The crude product was purified by column chromatography on a Biotage Isolera Flash Purification System (R_f = 0.53 in hexanes). Colorless oil (72 mg, 57% yield). ^{19}F NMR (377 MHz, $CDCl_3$): δ −62.3. HRMS EI [M^+] calcd for $C_{13}H_9F_3S$, 254.0371; found, 254.0383. ^{1}H and ^{13}C NMR data matched those reported in the literature.[40]

*Bis(4-bromophenyl) Sulfide (**15**).* The crude product was purified by distillation (bp = 411 °C at 760 Torr). Clear oil (100 mg, 58% yield). HRMS EI [M^+] calcd for $C_{12}H_8Br_2S$, 341.8713; found, 341.8721. ^{1}H and ^{13}C NMR data matched those reported in the literature.[41]

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra of all compounds and experiments used to assess the possibility of a radical mechanism. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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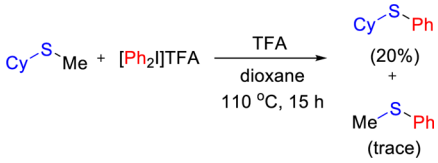
(27) For example, see the following:



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(33) Isolated butyl diphenyl sulfonium trifluoroacetate ($Ph_2SBuTFA$) was completely insoluble under our reaction conditions. Only 5% yield of Ph_2S could be detected after reaction.
(34) We predict that the mass balance for the butyl fragment is likely accounted for by butene, which would be formed via elimination from butyl trifluoroacetate or the sulfonium intermediate. No other butyl-containing products were observed by GC−MS analysis of the crude reaction mixture.
(35) Experiments using the radical traps (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl (TEMPO) and butylhydroxytoluene (BHT) were also performed. The results, which show that there is no inhibition by these reagents, are included in the Supporting Information.
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