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Waste-Free Swift Synthesis of Symmetrical and Unsymmetrical Diarylmethyl Thioethers from Diaryl Carbinols

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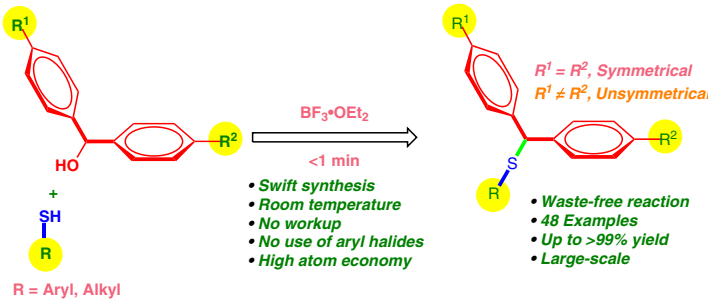

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Abstract A waste-free and swift protocol to synthesize symmetrical and unsymmetrical diarylmethyl thioethers from diaryl carbinols and thiols in good to quantitative yields is reported. The thiol scope included alkyl and aryl thiols bearing electron-donating and electron-withdrawing groups. Short reaction time, high atom economy, inexpensive activator, free from workup and aryl halides, and gram-scale synthesis are the significant features of the new protocol.

Key words thioetherification, diarylmethyl thioethers, diaryl, carbinols, high atom economy, Lewis acid activator

Part of the renaissance in C–heteroatom bond formation, the C–S bond has enjoyed a special status and focus on its activation.[1] Highly selective functionalization of the C–S bond can accurately modify sulfur-containing molecules.[2] Organosulfur compounds are in great demand as intermediates for the synthesis of bioactive natural products and often possess therapeutic activities.[3] Sulfides are particularly attractive sources of carbon centered radicals due to their reactivity and stability.[4] The biaryl sulfides are important structural motifs for several drugs, which are used against Alzheimer's, Parkinson's, malarial, inflammatory, HIV, and cancer diseases.[5] Among the sulfur-derived functional groups, thioethers[6] (e.g., cephalosporin analogues), their derived sulfoxides[7] (e.g., armodafinil, omeprazole, and ajoene) and sulfones[8] (e.g., dapsone) have been effectively used in research areas of medicinal chemistry and human health care.[6–8] Bunch of thioethers and sulfones are being harnessed as synthons for the synthesis of novel products for human needs and more valuable materials.[9] Along these lines, modern synthetic chemists have efficiently used thioethers as prominent organocatalysts and good ligands in transition-metal catalysis.[10]

Novel approaches to break and form carbon–heteroatom bonds provide opportunities to develop new protocols and to expand the chemist's synthetic repertoire.[11] Example applications of thioethers in organic synthesis are illustrated in Figure 1. Among the wide-spread category of thioethers, benzhydryl thioethers serve as appropriate probes in enzymatic and biomimetic oxidation processes to test the intermediacy of radical cations.[12] The metal-catalyzed arylation of C–H bonds in benzyl thioethers was demonstrated as an unprecedented approach to synthesize diaryl sulfides.[13] Recently, synthetic chemists have employed stable aryl diphenylmethyl sulfides for the investigation of electron-transfer–oxygen-transfer mechanism.[14] Olah and co-workers reported the formation of C–F bonds through the oxidative desulfurative fluorination of phenyl sulfides.[15]

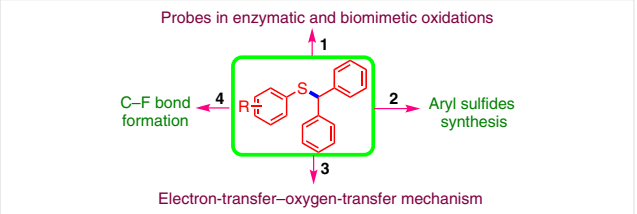


Figure 1 Applications of diarylmethyl thioethers

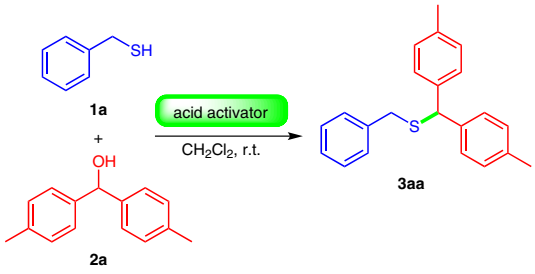
To date, several methods for synthesizing thioethers, mainly involving catalytic strategies, have proven successful.[16] Despite the exploration of numerous transformations for making C–S bonds, these methods have considerable limitations in important areas of research because sulfur easily undergoes oxidative formation of the undesired S–S bond, leading to disulfide by-products.[17] Sulfur has strong coordinating ability with metals, which deactivates the metal catalysts when compared to C–N and C–O bond formation.[18] A couple of reports demonstrated that diarylmethyl thioethers have also been prepared by using protic

ionic liquids[19] and silica-supported perchloric acid[20] but these methods suffer from limitation of toxicity and harsh reaction conditions, are expensive, and require additional steps for the synthesis of the catalyst. Over several years, much of the work has been devoted to thioether synthesis through the cross-coupling of thiols with aryl halides where transition metals such as nickel,[21] cobalt,[22] palladium,[23] and iron[24] have been found as excellent catalysts for this purpose. Copper and copper-based enzyme laccase are better at catalyzing the reactions in most cases.[25] The *N*-chlorosuccinimide was implemented by Lee and co-workers in a remarkable synthesis of aryl sulfides via thioetherification reaction of thiols and corresponding Grignard reagents with suitable metals.[26] Considerable limitations of these methods in the cross-coupling of thiols with aryl halides have shown serious issues to synthetic chemists. A drawback of Pd, Cu, Co, and Ni catalysts is the requirement for long reaction time, high reaction temperature, low sensitivity, tedious workup procedures, and their associated toxicity, which may limit the wide application of these catalysts. To this need, the judicious design of new methods involving less energy, inexpensive precursors, and the use of cheap, eco-friendly, and easily available catalysts are highly desirable in this area of research.

The electron acceptor boron trifluoride has been receiving more and more attention due to its strong Lewis acid character. Among the Lewis acids, $BF_3{\cdot}OEt_2$ is a very reactive adduct of BF_3 and Et_2O through sigma-bonding.[27] In recent years, $BF_3{\cdot}OEt_2$ based activation has provided a powerful avenue in modern organic synthesis where it is employed in alkylation, cyclization, rearrangement, Michael addition, and coupling reactions.[28] Interest in $BF_3{\cdot}OEt_2$-catalyzed transformations has blossomed because of its eco-friendly nature, efficient reactivity, and low cost. Although several diverse approaches have been reported for the synthesis of diarylmethyl thioethers, the development of sustainable and practical synthetic protocol is still an attractive goal for synthetic practitioner. In this context, with the advent of advancement in diaryl carbinols chemistry,[29] we herein report a waste-free, direct, and swift synthesis of symmetrical diarylmethyl thioethers (SDAMTs) and unsymmetrical diarylmethyl thioethers (*un*SDAMTs) by using simple and easily available $BF_3{\cdot}OEt_2$ via dehydrative S_N1 reaction.

Given the importance to benzhydryl alcohols, which can be activated under mild conditions using Lewis acids or Brønsted acids and liberate water as by-product,[30] we embarked our study with the synthesis of diaryl carbinols with the known procedure.[31] Identifying the suitable activator for the synthesis of symmetrical and unsymmetrical diarylmethyl thioethers is an important task. For this purpose, benzyl mercaptan (**1a**) and di-(*p*-tolyl)methanol (**2a**) were selected in the presence of various acid activators in dichloromethane at room temperature as a model system. In our preliminary studies, the reaction proceeded smoothly under the influence of triflic acid and the product was obtained in good yield (70%) (Table 1, entry 1). Further, we moved for the optimization of reaction conditions. Interestingly, it was found that 20 mol% of Brønsted acids *p*-TSA·H_2O and trifluoroacetic acid worked effectively to furnish **3aa** in enhanced yield of 75–78% (entries 2 and 3). On screening with Lewis acids such as $SnCl_4$, $FeCl_3$, and $ZrCl_4$, the reaction was found to be complete within minutes and good amount (82–87%) of product was isolated (entries 4–6).

Table 1 Optimization of Reaction Conditions[a]



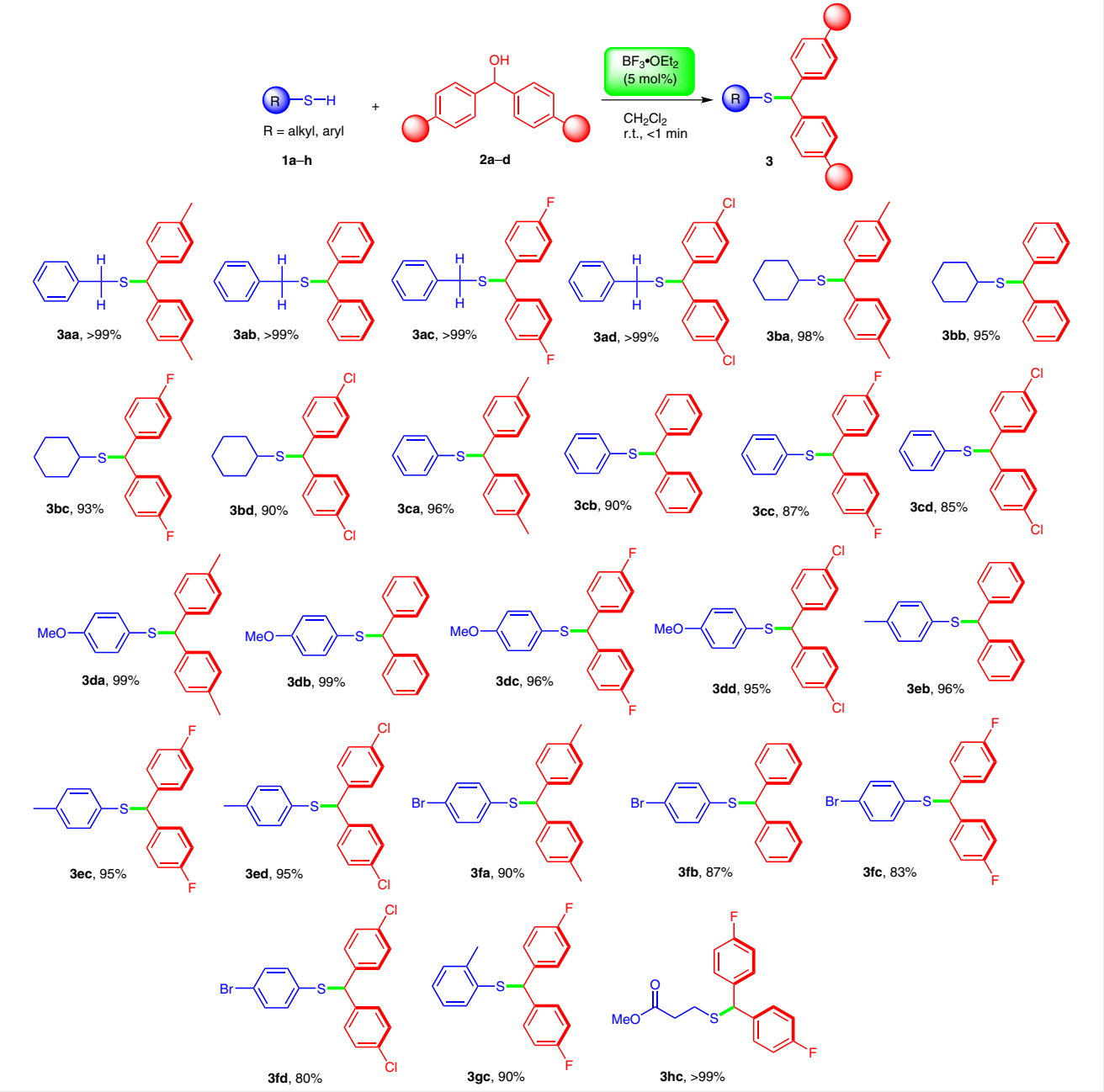
Entry	Activator (mol%)	Time (min)	Yield (%)[b]
1	TfOH (20)	100	70
2	*p*-TSA·H_2O (20)	60	75
3	TFA (20)	60	78
4	$SnCl_4$ (20)	20	82
5	$FeCl_3$ (20)	20	87
6	$ZrCl_4$ (20)	20	87
7	I_2 (20)	10	75
8	$BF_3{\cdot}OEt_2$ (20)	<1	>99
9	$BF_3{\cdot}OEt_2$ (10)	<1	>99
10	$BF_3{\cdot}OEt_2$ (5)	<1	>99

[a] Reactions of **1a** (0.5 mmol) with **2a** (0.6 mmol) in the presence of various activator were carried out in 2 mL of CH_2Cl_2.
[b] Yield of pure and isolated products.

Surprisingly molecular iodine enhanced the rate of reaction albeit with diminished yield of the product as **1a** readily undergoes oxidative S–S bond formation (Table 1, entry 7). During the screening process, 20 mol% of $BF_3{\cdot}OEt_2$ pleasantly furnished the thioether **3aa** in quantitative yield within seconds (entry 8). Then the model reaction was examined to check the impact of the quantity of $BF_3{\cdot}OEt_2$ on the reaction yield and time. Decreasing the loading of $BF_3{\cdot}OEt_2$ from 20 mol% to 5 mol% had no obvious effect on yield and rate of the reaction (entries 9 and 10). This screening led to the identification that $BF_3{\cdot}OEt_2$ affords the product **3aa** without any impurities or side products within seconds.

Once the optimal conditions were established with the identification of suitable activator for the facile synthesis of diarylmethyl thioether, the scope of this swift protocol was probed to a range of aliphatic and aromatic thiols with diaryl carbinols (Scheme 1). Thus the reaction of **1a** with diphenyl carbinol (**2b**) and other alcohols **2c** and **2d**, bearing electron-withdrawing halo groups, furnished thioethers **3ab**, **3ac**, and **3ad** in quantitative yield. Further, the reactivity of cyclohexanethiol (**1b**) was examined with **2a–d** for this transformation, which yielded the products **3ba**, **3bb**, **3bc**, and **3bd** in excellent yields (90–98%).

When parent thiophenol was employed in the reaction with alcohols **2a–d**, the products **3ca**, **3cb**, **3cc**, and **3cd** were obtained in 85–96% yield. To extend the substrate scope of the developed protocol we used 4-methoxythiophenol (**1d**) and 4-methylthiophenol (**1e**) as nucleophiles in combination with diarylcarbinols **2a–d**. Delightedly, the



Scheme 1 Scope for waste-free synthesis of symmetrical diarylmethyl thioethers. *Reagents and conditions*: Thiol **1** (0.5 mmol), diarylcarbinol **2** (0.6 mmol), $BF_3{\cdot}OEt_2$ (5 mol%), CH_2Cl_2 (2 mL).

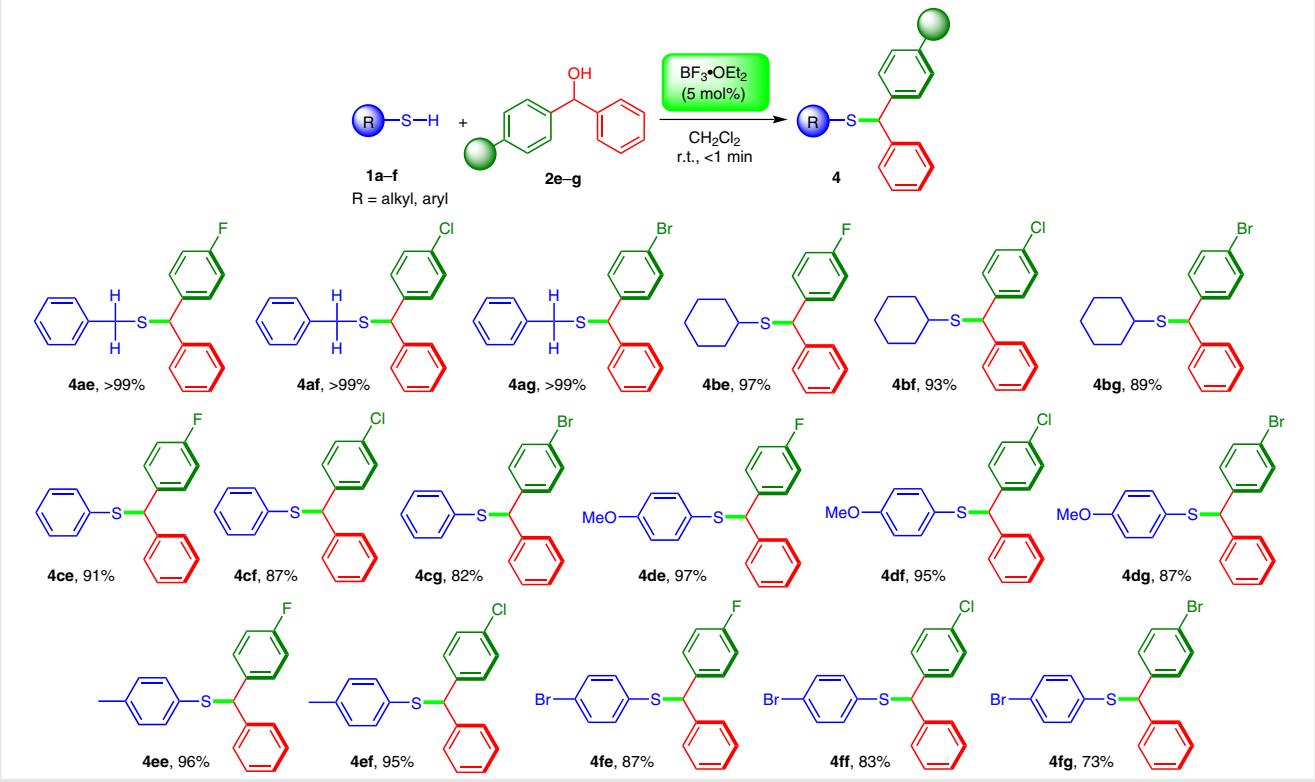
SDAMTs **3da–dd** and **3eb–ed** were isolated in excellent to quantitative yields. Encouraged by these results, thiol **1f** bearing electron-withdrawing bromo group at 4-position was investigated for this expeditious protocol and the corresponding SDAMT products **3fa–fd** were achieved in high yields. Thiols such as *o*-thiocresol (**1g**) and methyl mercaptopropionate (**1h**) worked well with bis(4-fluorophenyl)methanol (**2c**) under optimized conditions to produce the thioethers **3gc** and **3hc** in excellent yield.

With the promising results in hand, we next extended the current protocol to synthesize *un*SDAMTs. This protocol shows the generality of diaryl carbinols **2e–g** having phenyl and monosubstituted phenyl groups with various alkyl and aryl thiols (Scheme 2). Variation of halo groups at 4-position of monosubstituted diaryl secondary alcohols was found to be tolerable with benzenemethanethiol (**1a**) and resulted in the products **4ae–ag** in quantitative yield. When cyclohexanethiol was submitted for *un*SDAMT products under our standard conditions, the diarylcarbinols **2e–g** resulted in the formation of thioethers **4be–bf** in very good to excellent yields (89–97%).

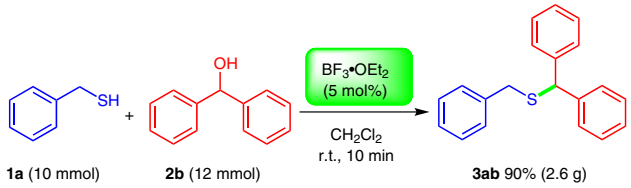
The importance of waste-free protocol was further explored by employing the parent thiophenol (**1c**) and electron-rich thiols **1d** and **1e** with **2e–g** under aforementioned conditions, which afforded *un*SDMATs, **4ce–cg**, **4de–dg**, **4ee**, and **4ef** in good to excellent yields ranging from 85–98%. 4-Bromothiophenol (**1f**) was also easily provided the thioethers **4fe–fg** in very good yields within seconds.

Afterwards, diaryl carbinols bearing *ortho*- and *meta*-substituted phenyl groups and even a 2,4-disubstituted phenyl group were employed as substrates to examine the feasibility of this methodology (Figure 2). Benzyl mercaptan (**1a**) was found to be ideal reaction partner with **2h** and **2i** affording the products **5ah** and **5ai** in quantitative yields. When methyl mercaptopropionate was subjected to this protocol, the products **5hi** and **5hj** were obtained in excellent to quantitative yields. In addition to alkyl thiols, when *o*-thiocresol (**1g**) was the choice of substrate in this swift protocol, the unsymmetrical thioether **5gh** was isolated in 91% yield. 4-Nitrothiophenol was also found to be an ideal precursor for this transformation, giving rise to **5ii** in 83% yield.

Inspired by above results and environmentally benign approach, the present method was evaluated for the gram-scale synthesis. The reaction between **1a** and **2b** was then conducted at 10 mmol level, which furnished benzhydryl(benzyl)sulfane (**3ab**) in quite a good amount (2.6 g; 90%) (Scheme 3). This confirmed the utility of elegant protocol in the gram-scale preparation of diarylmethyl thioethers.



Scheme 2 Scope for waste-free synthesis of unsymmetrical diarylmethyl thioethers. *Reagents and conditions*: Thiol **1** (0.5 mmol), diaryl carbinol **2** (0.6 mmol), $BF_3{\cdot}OEt_2$ (5 mol%), CH_2Cl_2 (2 mL).



Scheme 3 Gram-scale synthesis of thioether **3ab**

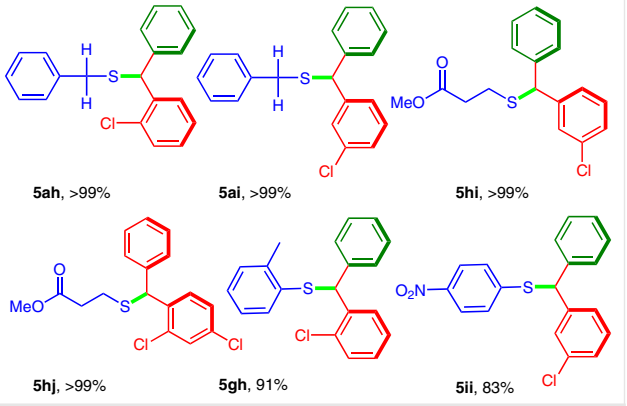
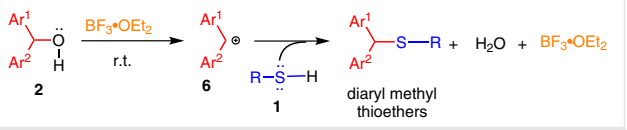


Figure 2 Scope for waste-free synthesis of unsymmetrical diarylmethyl thioethers. *Reaction conditions*: Thiol **1** (0.5 mmol), diaryl carbinol **2** (0.6 mmol), $BF_3{\cdot}OEt_2$ (5 mol%), CH_2Cl_2 (2 mL), <1 min (cf. Schemes 1 and 2).

As the present methodology holds the advantage of easy operation, nontoxic, allows the use of readily available and inexpensive catalyst as well as direct use of diaryl carbinols, free from workup and waste release, and water is the only by-product, this is a more attractive method than the reported methods. Therefore, to the best of our knowledge, this is the first ever report on thiolation of diaryl carbinols that use $BF_3{\cdot}OEt_2$ as a catalyst to accomplish the merging of diaryl carbinols with thiols.

Based on the above experimental results and related literature reports[32] these reactions presumably proceed via dehydrative S_N1 mechanism (Scheme 4). A benzyl carbocation **6** might be formed from diaryl carbinol **2** in the presence of $BF_3{\cdot}OEt_2$ and then **6** could be attacked by thiol **1** to afford the product diarylmethyl thioether.



Scheme 4 Plausible reaction mechanism

In summary, we have reported a novel, waste-free, and swift synthesis of symmetrical and unsymmetrical diarylmethyl thioethers with high atom economy. The developed methodology is highly efficient and practical due to the use of inexpensive $BF_3{\cdot}OEt_2$ as a catalyst and easily available precursors. The level of success in the swift reaction is somewhat dependent on the thiophenol nucleophilicity and the substituents on benzhydryl alcohols. It was also observed that bromo substitution on the thiol decreased the yield in the reaction. Nevertheless, the direct thiophenol-into-thioether conversion constitutes a powerful track for the high-yielding synthesis of diarylmethyl thioethers. Metal-free conditions, broad substrate scope with diverse substitution patterns, large-scale preparation, and operational simplicity are noteworthy features of this economic synthetic process.

All obtained symmetrical and unsymmetrical diarylmethyl thioethers were fully characterized. Synthesis of all diarylmethyl thioethers were carried out at r.t. Commercially available chemicals were purchased from commercial vendors in highest purity grade and used directly for waste-free protocol without further purification. All syntheses were performed in standard glassware without any special precautions taken for the removal of moisture or air. CH_2Cl_2 was purified by distillation over the P_2O_5. Merck precoated 0.25 mm silica gel plates (60F-254) were used to perform the analytical TLC. Visualization was achieved with short wave UV light. Eluting solvents are mentioned in the general procedure for synthesis. Column chromatography was carried out with silica gel (100–200 mesh) using EtOAc/hexanes. ^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on Jeol spectrometer, respectively. Chemical shift in ^1H NMR is referenced internally to residual solvent peak (δ = 7.26) as internal standard in $SiMe_4$ (δ = 0.00) ppm. ^{13}C NMR spectra were referenced to $CDCl_3$ (δ = 77.0, the middle peak). Chemical shifts (δ) are reported as ppm in δ scale downfield from TMS. Coupling constants are expressed in Hz. The multiplicity was explained by standard abbreviations. Melting points were recorded on a Perfit melting point instrument and are uncorrected.

Symmetrical and Unsymmetrical Diarylmethyl Thioethers; General Procedure

To a solution of thiol **1** (0.5 mmol) in anhyd CH_2Cl_2 (2 mL) was added diaryl carbinol **2** (0.6 mmol) and $BF_3{\cdot}OEt_2$ (5 mol% solution in CH_2Cl_2; 1 mL). The reaction mixture was stirred vigorously for <1 min. After completion of the reaction as checked by TLC, the solvent was removed under reduced pressure, and the residue was subjected to silica gel column chromatography by using 5–10% EtOAc in hexanes to afford the desired symmetrical and unsymmetrical diarylmethyl thioether in good to quantitative yield.

Benzyl[di(*p*-tolyl)methyl]sulfane (3aa)

Yield: 157 mg (>99%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 9 H), 7.14–7.12 (m, 4 H), 4.93 (s, 1 H), 3.57 (s, 2 H), 2.34 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.38, 138.29, 136.85, 129.39, 129.17, 128.54, 128.45, 127.02, 52.79, 36.72, 21.20.

Benzhydryl(benzyl)sulfane (3ab)

Yield: 134 mg (>99%); white solid; mp 72–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.43 (m, 5 H), 7.35–7.33 (m, 6 H), 7.3–7.26 (m, 4 H), 5.00 (s, 1 H), 3.60 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.12, 138.08, 129.17, 128.71, 128.60, 127.32, 127.12, 53.30, 36.17.

Benzyl[bis(4-fluorophenyl)methyl]sulfane (3ac)

Yield: 155 mg (>99%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 9 H), 7.08–7.03 (m, 4 H), 4.98 (s, 1 H), 3.60 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.0 (d, *J* = 245.0 Hz, CF), 137.79, 136.75, 136.72, 130.19, 130.11, 129.05, 128.64, 127.27, 115.62 (d, *J* = 29.4 Hz), 51.73, 36.52.

Benzyl[bis(4-chlorophenyl)methyl]sulfane (3ad)

Yield: 178 mg (>99%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31–7.24 (m, 11 H), 7.19–7.17 (m, 2 H), 4.83 (s, 1 H), 3.54 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.16, 137.54, 133.25, 129.84, 129.05, 128.91, 128.63, 127.30, 57.80, 36.69.

Cyclohexyl[di(*p*-tolyl)methyl]sulfane (3ba)

Yield: 152 mg (98%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.41 (m, 4 H), 7.21–7.19 (m, 4 H), 5.31 (s, 1 H), 2.63–2.56 (m, 1 H), 2.40 (s, 6 H), 2.40–2.00 (m, 2 H), 1.82–1.80 (m, 2 H), 1.64–1.59 (m, 1 H), 1.54–1.45 (m, 2 H), 1.36–1.27 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.42, 136.60, 129.36, 128.30, 52.0, 43.62, 33.46, 26.13, 25.98, 21.26.

Benzhydryl(cyclohexyl)sulfane (3bb)

Yield: 134 mg (95%); white solid; mp 64–66 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.40 (m, 4 H), 7.30–7.26 (m, 4 H), 7.22–7.17 (m, 2 H), 5.22 (s, 1 H), 2.50–2.43 (m, 1 H), 1.90–1.87 (m, 2 H), 1.71–1.68 (m, 2 H), 1.54–1.51 (m, 1 H), 1.40–1.32 (m, 2 H), 1.25–1.22 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.07, 128.60, 128.38, 127.08, 52.49, 43.65, 33.35, 25.97, 25.90.

[Bis(4-fluorophenyl)methyl](cylohexyl)sulfane (3bc)

Yield: 148 mg (93%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 4 H), 7.00 (t, *J* = 8.8 Hz, 4 H), 5.22 (s, 1 H), 2.49–2.42 (m, 1 H), 1.91–1.87 (m, 2 H), 1.73–1.71 (m, 2 H), 1.56–1.54 (m, 1 H), 1.42–1.33 (m, 2 H), 1.24–1.15 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.88 (d, *J* = 244.7 Hz, CF), 137.65, 129.87, 129.78, 115.50 (d, *J* = 21.9 Hz), 100.0, 50.93, 43.78, 33.28, 25.88.

[Bis(4-chlorophenyl)methyl](cylohexyl)sulfane (3bd)

Yield: 158 mg (90%); white solid; mp 66–68 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45 (d, *J* = 8.0 Hz, 3 H), 7.31 (t, *J* = 7.6 Hz, 3 H), 7.24–7.20 (m, 2 H), 5.26 (s, 1 H), 2.53–2.46 (m, 1 H), 1.95–1.91 (m, 2 H), 1.75–1.72 (m, 2 H), 1.57–1.54 (m, 1 H), 1.44–1.35 (m, 2 H), 1.29–1.15 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.09, 128.62, 128.40, 127.10, 52.56, 43.66, 33.37, 25.99, 25.92.

[Di-(*p*-tolyl)methyl](phenyl)sulfane (3ca)

Yield: 146 mg (96%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.0 Hz, 4 H), 7.25–7.23 (m, 2 H), 7.20–7.09 (m, 7 H), 5.51 (s, 1 H), 2.31 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.31, 136.91, 136.69, 130.14, 129.33, 128.78, 128.30, 126.37, 56.76, 21.17.

Benzhydryl(phenyl)sulfane (3cb)

Yield: 124 mg (90%); white solid; mp 67–68 °C (Lit.[33] mp 66–68 °C).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.39 (m, 4 H), 7.30–7.11 (m, 11 H), 5.23 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.09, 136.22, 130.60, 128.82, 128.64, 128.51, 127.36, 127.67, 57.52.

[Bis(4-fluorophenyl)methyl](phenyl)sulfane (3cc)

Yield: 135 mg (87%); white solid; mp 68–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.36 (m, 4 H), 7.24–7.18 (m, 5 H), 7.01 (t, *J* = 8.8 Hz, 4 H), 5.53 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.03 (d, *J* = 245.0 Hz, CF), 136.70, 136.65, 135.50, 131.02, 130.09, 130.0, 128.96, 127.09, 115.58 (d, *J* = 29.5 Hz), 56.13.

[Bis(4-chlorophenyl)methyl](phenyl)sulfane (3cd)

Yield: 146 mg (85%); white solid; mp 72–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.17 (m, 13 H), 5.47 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.19, 135.22, 133.38, 131.08, 129.81, 129.05, 128.91, 127.25, 56.37.

[Di(*p*-tolyl)methyl](4-methoxyphenyl)sulfane (3da)

Yield: 165 mg (99%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.29 (m, 4 H), 7.25–7.23 (m, 2 H), 7.12 (d, *J* = 11.2 Hz, 4 H), 6.75 (d, *J* = 8.8 Hz, 2 H), 5.35 (s, 1 H), 3.76 (s, 3 H), 2.33 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.24, 138.65, 136.76, 134.36, 129.25, 128.32, 126.51, 114.37, 58.72, 55.37, 21.18.

Benzhydryl(4-methoxyphenyl)sulfane (3db)

Yield: 151 mg (99%); white solid; mp 89–90 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.47–7.45 (m, 4 H), 7.36–7.26 (m, 8 H), 6.79 (d, *J* = 8.4 Hz, 2 H), 5.42 (s, 1 H), 3.81 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.41, 141.39, 134.83, 128.29, 128.10, 127.42, 125.83, 114.38, 65.63, 55.25.

[Bis(4-fluorophenyl)methyl](4-methoxyphenyl)sulfane (3dc)

Yield: 164 mg (96%); white solid; mp 75–77 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.30 (m, 4 H), 7.19 (d, *J* = 8.8 Hz, 2 H), 6.98 (t, *J* = 8.8 Hz, 4 H), 6.74 (d, *J* = 8.8 Hz, 2 H), 5.32 (s, 1 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.24 (t, *J* = 245.0 Hz, CF), 137.04, 137.02, 135.14, 130.14, 130.07, 125.36, 115.61, 115.50 (d, *J* = 21.0 Hz), 114.56, 57.95, 55.41.

[Bis(4-chlorophenyl)methyl](4-methoxyphenyl)sulfane (3dd)

Yield: 177 mg (95%); white solid; mp 68–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.21 (m, 10 H), 6.76 (d, *J* = 8.4 Hz, 2 H), 5.37 (s, 1 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.66, 139.41, 135.12, 133.10, 129.77, 128.69, 124.93, 114.45, 58.06, 55.28.

Benzhydryl(*p*-tolyl)sulfane (3eb)

Yield: 139 mg (96%); white solid; mp 60–62 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.16 (m, 10 H), 7.11 (d, *J* = 8.0 Hz, 2 H), 6.97 (d, *J* = 8.0 Hz, 2 H), 5.44 (s, 1 H), 2.33 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.30, 141.29, 136.87, 132.35, 131.40, 129.57, 128.55, 127.24, 58.11, 21.17.

[Bis(4-fluorophenyl)methyl](*p*-tolyl)sulfane (3ec)

Yield: 155 mg (95%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.35 (m, 4 H), 7.22–7.20 (m, 2 H), 7.12–7.04 (m, 6 H), 5.51 (s, 1 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.96 (d, *J* = 245.0 Hz, CF), 137.40, 136.86, 131.81, 131.59, 130.06, 129.97, 129.71, 115.48 (d, *J* = 21.0 Hz), 56.69, 21.16.

[Bis(4-chlorophenyl)methyl](*p*-tolyl)sulfane (3ed)

Yield: 170 mg (95%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.19 (m, 8 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 5.36 (s, 1 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.19, 137.38, 133.22, 133.07, 131.71, 131.13, 129.60, 128.62, 56.76, 20.96.

(4-Bromophenyl)[di(*p*-tolyl)methyl]sulfane (3fa)

Yield: 172 mg (90%); white solid; mp 96–98 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26–7.23 (m, 6 H), 7.08–7.03 (m, 6 H), 5.44 (s, 1 H), 2.28 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.78, 137.13, 135.77, 131.66, 129.42, 129.34, 128.28, 120.36, 56.80, 21.17.

Benzhydryl(4-bromophenyl)sulfane (3fb)

Yield: 154 mg (87%); white solid; mp 108–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.38 (m, 4 H), 7.30–7.20 (m, 8 H), 7.06 (d, *J* = 8.4 Hz, 2 H), 5.49 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.58, 135.29, 132.15, 131.87, 128.72, 128.45, 127.52, 120.72, 57.54.

[Bis(4-fluorophenyl)methyl](4-bromophenyl)sulfane (3fc)

Yield: 162 mg (83%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 6 H), 7.07–6.95 (m, 6 H), 5.47 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.12 (d, *J* = 245.0 Hz, CF), 137.60, 136.27, 134.66, 132.58, 132.07, 130.11, 130.03, 128.85, 121.26, 115.64 (t, *J* = 21.5 Hz), 79.01, 56.19.

[Bis(4-chlorophenyl)methyl](4-bromophenyl)sulfane (3fd)

Yield: 170 mg (80%); white solid; mp 82–85 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.20 (m, 10 H), 7.05 (d, *J* = 8.0 Hz, 2 H), 5.40 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.59, 133.19, 132.47, 131.48, 131.01, 128.64, 127.90, 120.30, 55.28.

[Bis(4-fluorophenyl)methyl](*o*-tolyl)sulfane (3gc)

Yield: 141 mg (90%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.32 (m, 4 H), 7.15–6.96 (m, 8 H), 5.46 (s, 1 H), 3.0 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.25, 160.80, 138.33, 136.64, 134.85, 130.26, 130.06, 129.98, 126.71, 126.48, 115.68, 115.46, 54.97, 20.50.

Methyl 3-[Bis(4-fluorophenyl)methyl]thiopropanoate (3hc)

Yield: 160 mg (>99%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.34 (m, 4 H), 7.0 (t, *J* = 8.4 Hz, 4 H), 5.18 (s, 1 H), 3.68 (s, 3 H), 2.65 (t, *J* = 7.2 Hz, 2 H), 2.54 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.30, 163.24, 160.79, 136.74, 136.71, 129.94, 129.86, 115.75, 115.54, 52.79, 51.96, 34.10, 27.27.

Benzyl[(4-fluorophenyl)(phenyl)methyl]sulfane (4ae)

Yield: 152 mg (>99%); white solid; mp 48–50 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ =7.41–7.24 (m, 12 H), 7.03 (t, *J* = 8.8 Hz, 2 H), 4.96 (s, 1 H), 3.59 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.97 (d, *J* = 244.0 Hz, CF), 140.92, 137.94, 136.94, 130.23, 129.13, 128.80, 128.62, 128.53, 115.53 (d, *J* = 22.0 Hz), 52.50, 36.74.

Benzyl[(4-chlorophenyl)(phenyl)methyl]sulfane (4af)

Yield: 161 mg (>99%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.24 (m, 14 H), 4.96 (s, 1 H), 3.61 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.69, 139.80, 137.90, 133.09, 130.14, 129.24, 128.92, 128.84, 128.66, 128.53, 127.57, 127.29, 52.57, 36.30.

Benzyl[(4-bromophenyl)(phenyl)methyl]sulfane (4ag)

Yield: 183 mg (>99%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ =7.46–7.44 (m, 2 H), 7.37–7.31 (m, 6 H), 7.28–7.22 (m, 6 H), 4.90 (s, 1 H), 3.56 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.55, 140.28, 137.82, 131.79, 130.36, 129.13, 128.82, 128.63, 128.50, 127.54, 127.24, 121.19, 52.65, 36.72.

Cyclohexyl[(4-fluorophenyl)(phenyl)methyl]sulfane (4be)

Yield: 145 mg (97%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.35 (m, 4 H), 7.30–7.26 (m, 2 H), 7.22–7.17 (m, 1 H), 6.96 (t, *J* = 8.8 Hz, 2 H), 5.19 (s, 1 H), 2.46–2.39 (m, 1 H), 1.88–1.85 (m, 2 H), 1.70–1.67 (m, 2 H), 1.53–1.51 (m, 1 H), 1.38–1.30 (m, 2 H), 1.23–1.11 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.83 (d, *J* = 244.0 Hz, CF), 141.84, 137.83, 129.94, 129.85, 128.66, 128.26, 127.21, 115.39 (d, *J* = 21.0 Hz), 51.74, 43.71, 33.33, 25.89.

Cyclohexyl[(4-chlorophenyl)(phenyl)methyl]sulfane (4bf)

Yield: 147 mg (93%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 4 H),7.34–7.28 (m, 4 H), 7.24–7.17 (m, 1 H), 5.24 (s, 1 H), 2.54–2.46 (m, 1 H), 1.94–1.91 (m, 2 H), 1.76–1.72 (m, 2 H), 1.57–1.55 (m, 1 H), 1.45–1.36 (m, 2 H), 1.28–1.20 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.61, 140.74, 132.83, 129.81, 128.77, 128.72, 128.31, 127.30, 51.90, 43.78, 33.36, 25.96, 25.91.

Cyclohexyl[(4-bromophenyl)(phenyl)methyl]sulfane (4bg)

Yield: 161 mg (89%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 4 H),7.30–7.28 (m, 4 H), 7.21–7.18 (m, 1 H), 5.17 (s, 1 H), 2.49–2.42 (m, 1 H), 1.89–1.86 (m, 2 H), 1.70–1.68 (m, 2 H), 1.54–1.52 (m, 1 H), 1.40–1.31 (m, 2 H), 1.24–1.15 (m, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.61, 140.74, 132.83, 129.81, 128.77, 128.72, 128.31, 127.30, 51.90, 43.78, 33.36, 25.96, 25.91.

[(4-Fluorophenyl)(phenyl)methyl](phenyl)sulfane (4ce)

Yield: 134 mg (91%); white solid; mp 71–73 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.28 (m, 4 H), 7.22–7.20 (m, 2 H), 7.17–7.10 (m, 6 H), 6.95 (t, *J* = 8.4 Hz, 2 H), 5.50 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.99 (d, *J* = 245.0 Hz, CF), 140.86, 136.90, 135.85, 130.84, 130.07, 128.89, 128.72, 128.41, 127.49, 126.88, 115.47 (d, *J* = 21.0 Hz), 56.84.

[(4-Chlorophenyl)(phenyl)methyl](phenyl)sulfane (4cf)

Yield: 135 mg (87%); white solid; mp 55–57 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.13 (m, 14 H), 5.50 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.59, 139.71, 135.71, 133.12, 130.97, 130.70, 129.88, 128.86, 128.65, 128.43, 127.69, 127.08, 56.98.

[(4-Bromophenyl)(phenyl)methyl](phenyl)sulfane (4cg)

Yield: 145 mg (82%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.36 (m, 4 H), 7.31–7.12 (m, 10 H), 5.48 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.37, 139.10, 134.56, 130.61, 129.69, 129.12, 127.83, 127.66, 127.29, 126.48, 125.84, 120.14, 55.85.

[(4-Fluorophenyl)(phenyl)methyl](4-methoxyphenyl)sulfane (4de)

Yield: 157 mg (97%); white solid; mp 63 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.16 (m, 9 H), 6.94 (t, *J* = 8.8 Hz, 2 H), 6.71 (d, *J* = 8.8 Hz, 2 H), 5.31 (s, 1 H), 3.73 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.13 (t, *J* = 246.0 Hz, CF), 141.21, 137.29, 134.96, 132.80, 130.19, 130.11, 128.64, 128.45, 127.39, 125.69, 115.35 (d, *J* = 21.0 Hz), 114.48, 58.67, 55.34.

[(4-Chlorophenyl)(phenyl)methyl](4-methoxyphenyl)sulfane (4df)

Yield: 162 mg (95%); white solid; mp 53 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 2 H), 7.33–7.20 (m, 9 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 5.33 (s, 1 H), 3.74 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.62, 140.90, 140.08, 134.98, 132.96, 129.95, 128.68, 128.45, 127.47, 125.54, 114.53, 58.78, 55.35.

[(4-Bromophenyl)(phenyl)methyl](4-methoxyphenyl)sulfane (4dg)

Yield: 167 mg (87%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.34 (m, 4 H), 7.31–7.19 (m, 7 H), 6.73 (d, *J* = 8.4 Hz, 2 H), 5.30 (s, 1 H), 3.75 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.58, 140.77, 140.56, 135.0, 131.32, 130.28, 128.67, 128.09, 127.41, 125.46, 121.09, 114.49, 58.78, 55.35.

[(4-Fluorophenyl)(phenyl)methyl](*p*-tolyl)sulfane (4ee)

Yield: 148 mg (96%); white solid; mp 53–55 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–6.92 (m, 12 H), 5.45 (s, 1 H), 2.27 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.94 (d, *J* = 245.0 Hz, CF), 141.09, 137.18, 132.01, 131.68, 130.18, 130.09, 129.68, 128.67, 128.43, 127.41, 115.40 (d, *J* = 21.0 Hz), 57.46, 21.15.

[(4-Chlorophenyl)(phenyl)methyl](*p*-tolyl)sulfane (4ef)

Yield: 154 mg (95%); white solid; mp 68–70 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 9 H), 7.12 (d, *J* = 8.0 Hz, 2 H), 6.98 (d, *J* = 8.0 Hz, 2 H), 5.41 (s, 1 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.77, 139.90, 133.0, 131.83, 131.71, 131.64, 129.93, 129.68, 128.74, 128.40, 127.45, 57.52, 21.19.

(4-Bromophenyl)[(4-fluorophenyl)(phenyl)methyl]sulfane (4fe)

Yield: 162 mg (87%); white solid; mp 70–72 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.22 (m, 9 H), 7.07 (d, *J* = 8.8 Hz, 2 H), 6.98 (d, *J* = 8.8 Hz, 2 H), 5.49 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.78 (d, *J* = 245.7 Hz, CF), 137.25, 135.88, 134.31, 132.19, 131.73, 129.77, 129.69, 128.58, 128.50, 120.90, 115.39 (d, *J* = 21.0 Hz), 55.80.

(4-Bromophenyl)[(4-chlorophenyl)(phenyl)methyl]sulfane (4ff)

Yield: 161 mg (83%); white solid; mp 72–74 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 11 H), 7.05 (d, *J* = 8.4 Hz, 2 H), 5.44 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.08, 139.18, 134.78, 133.31, 132.35, 132.0, 129.83, 128.88, 128.86, 128.37, 127.76, 121.06, 56.93.

(4-Bromophenyl)[(4-bromophenyl)(phenyl)methyl]sulfane (4fg)

Yield: 158 mg (73%); white solid; mp 80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.41 (m, 2 H), 7.37–7.23 (m, 9 H), 7.07 (d, *J* = 8.4 Hz, 2 H), 5.45 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.03, 139.75, 134.77, 132.40, 132.02, 131.83, 130.19, 128.86, 128.37, 127.77, 121.47, 121.10, 57.05.

Benzyl[(2-chlorophenyl)(phenyl)methyl]sulfane (5ah)

Yield: 161 mg (>99%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (d, *J* = 8.4 Hz, 1 H), 7.34–7.12 (m, 13 H), 5.43 (s, 1 H), 3.56 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.86, 138.42, 137.62, 133.98, 130.15, 129.81, 129.09, 128.71, 128.63, 128.56, 128.45, 127.38, 127.25, 127.16, 49.27, 37.01.

Benzyl[(3-chlorophenyl)(phenyl)methyl]sulfane (5ai)

Yield: 161 mg (>99%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 7 H), 7.24–7.19 (m, 7 H), 4.87 (s, 1 H), 3.53 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.26, 140.35, 137.73, 134.48, 129.09, 128.82, 128.67, 128.61, 128.51, 127.58, 127.50, 127.24, 126.79, 52.75, 36.71.

Methyl 3-[(3-Chlorophenyl)(phenyl)methyl]thiopropanoate (5hi)

Yield: 159 mg (>99%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.39 (m, 3 H), 7.34–7.20 (m, 3 H), 7.25–7.19 (m, 3 H), 5.16 (s, 1 H), 3.67 (s, 3 H), 2.67 (t, *J* = 7.2 Hz, 2 H), 2.55 (t, *J* = 4.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.34, 139.98, 138.69, 133.76, 130.03, 129.79, 128.71, 128.57, 127.52, 127.35, 51.94, 49.91, 34.23, 27.41.

Methyl 3-[(2,4-Dichlorophenyl)(phenyl)methyl]thiopropanoate (5hj)

Yield: 176 mg (>99%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, *J* = 8.0 Hz, 1 H), 7.32 (t, *J* = 8.4 Hz, 3 H), 7.23 (d, *J* = 8.4 Hz, 3 H), 7.14 (t, *J* = 7.6 Hz, 1 H), 5.66 (s, 1 H), 3.64 (s, 3 H), 2.67 (t, *J* = 7.2 Hz, 2 H), 2.56 (t, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.16, 138.64, 138.23, 133.75, 133.27, 129.86, 128.84, 128.79, 127.45, 51.92, 49.90, 34.19, 27.46.

[(2-Chlorophenyl)(phenyl)methyl](*o*-tolyl)sulfane (5gh)

Yield: 148 mg (91%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.41 (m, 3 H), 7.36–7.23 (m, 6 H), 7.18–7.02 (m, 4 H), 5.49 (s, 1 H), 2.40 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.28, 140.42, 138.40, 135.0, 134.49, 130.31, 130.27, 129.92, 128.85, 128.67, 128.48, 127.69, 127.62, 126.74, 126.56, 56.15, 20.58.

[(3-Chlorophenyl)(phenyl)methyl](4-nitrophenyl)sulfane (5ii)

Yield: 147 mg (83%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 9.2 Hz, 2 H), 7.43–7.39 (m, 3 H), 7.36–7.22 (m, 8 H), 5.68 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.26, 145.54, 141.62, 138.80, 134.92, 130.27, 129.18, 128.53, 128.35, 128.24, 127.48, 126.58, 124.01, 55.26.

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Supporting Information

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