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An Efficient Copper-Catalyzed Cross-Coupling Reaction of Thiols with Aryl Iodides

Hsin-Lun Kao,[a] Chin-Keng Chen,[a] Yu-Jen Wang,[a] and Chin-Fa Lee*[a]

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Commercially available Cu_2O powder is a very reactive catalyst for the coupling of thiols to aryl iodides. A variety of functional groups including esters, unprotected amines, alcohols, and heterocycles tolerate the reaction conditions. Moreover, di-*ortho*-substituted aryl iodides with sterically demanding substrates were also coupled to give the desired aryl thioethers in good to excellent yields.

Introduction

Transition-metal-catalyzed cross-coupling reactions of aryl halides with heteroatom nucleophiles are powerful methods for constructing carbon–heteroatom bonds.[1–4] While having access to aryl thioethers is important in the preparation of pharmaceutically and biologically relevant compounds, several challenges still remain.[5,6] As a result of the strong binding affinity of thiols for transition metals, the metal catalysts are often poisoned, leading to decreased activity.[7] Despite this unfavorable route, Migita reported the first palladium-catalyzed coupling reaction of thiols with aryl halides in 1980,[8] and more recent studies have revealed that the efficiency of the C–S coupling reaction can be improved through the combination of palladium with appropriate ligands.[9] Besides palladium, transition metals such as nickel,[10] iron,[11] indium,[12] cobalt,[13] and copper[14] have also been reported. These protocols rely on the presence of ancillary ligands, and recently, a metal-catalyzed coupling reaction under ligand-free conditions has gained considerable attention.[15–18] van Koten et al. reported the copper-catalyzed coupling reaction of aryl iodides in amide solvent[17,19] without a ligand.[16a] There are some limitations with van Koten's system. First, the thiols used were limited to aryl thiols; only one alkyl thiol was coupled with iodobenzene in moderate yield. Second, sterically bulky aryl iodides were not involved.

A variety of nanosurfaced materials have recently been considered as new catalysts for organic synthesis owing to their high surface area and high reactivity.[15] Commercially available CuO nanoparticles (surface area: 29 cm^2/g) were demonstrated to be active catalysts for C–S bond-forming reactions under ligand-free conditions;[17] however, there are some difficulties in this system: (1) CuO nanoparticles are expensive; (2) low yields were generally obtained when electron-rich aryl iodides were employed, and (3) highly polar solvents (DMSO) were required. More recently, In_2O_3 nanoparticles were reported to show similar catalytic activity, but they possess similar limitations at a higher cost.[18]

Thus, it is desirable to develop a general method that is capable of overcoming the aforementioned synthetic limitations and cost. Herein, we report that commercially available Cu_2O powder is a very reactive (0.5 mol-%) catalyst in combination with KOH or KOEt as the base for the coupling reaction of thiols with aryl iodides in the absence of an added ligand.

Results and Discussion

Initially, we screened 4-iodotoluene and 1-dodecanethiol as model substrates to determine optimal reaction conditions. The results are summarized in Table 1. KO*t*Bu[9c,9d,10b,11a,14h,14k] and NaO*t*Bu,[8a,9c–9e,11a,11b,14d,14i–14k] are commonly used as bases for C–S coupling reactions; however, when the reaction was carried out with KO*t*Bu in DMSO, a low yield of **3a** was obtained along with its regioisomer **4a** (Table 1, Entry 1; **3a**/**4a** = 92:8). Compound **4a** is the product of a benzyne intermediate, and similar reactivity has been observed in the copper-catalyzed arylation of arenes.[20] Although amide solvents have been shown to be effective in C–S coupling reactions, a low yield of **3a** (Table 1, Entry 2; **3a**/**4a** = 79:21) was observed when the reaction was performed in DMF. To our delight, good yields were obtained when reactions were carried out in DME (Table 1, Entry 3) and dioxane (Table 1, Entry 4; 86% isolated yield), and the formation of **4a** was totally suppressed under these conditions. To exclude the possibility of metal contaminants,[14i] the reaction was performed

[a] Department of Chemistry, National Chung Hsing University, Taichung, Taiwan 402, ROC, Taiwan
Fax: +886-4-2286-2547
E-mail: cfalee@dragon.nchu.edu.tw

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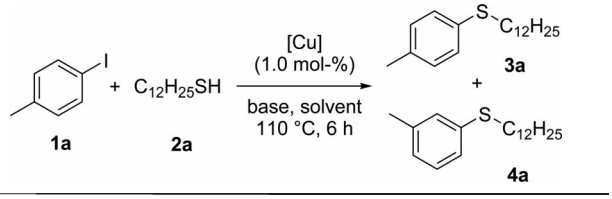
by using highly pure Cu_2O (>99.99%, Aldrich) as a metal source. Importantly, a comparable isolated yield (86%) rules out any trace metal impurity catalyzing the reaction (Table 1, Entry 5). Weaker bases such as KOEt, KOMe, KOH,[12] NaOH, K_3PO_4, and K_2CO_3[9b,14b] were examined (Table 1, Entries 6–14), and the results revealed that KOEt, KOMe, and KOH were more effective than KO*t*Bu, giving the product in excellent yields (Table 1, Entries 6, 7, and 8, respectively). The study of various copper salts (Table 1, Entries 15–17) demonstrated that Cu_2O is the most effective copper source. The mixture of **3a**/**4a** (74:26 ratio) was obtained in a low combined yield when the reaction was carried out without a catalyst (Table 1, Entry 18). No desired coupling product was detected when 4-iodotoluene was replaced by bromobenzene or chlorobenzene under the same conditions.

Table 1. Optimization of Cu_2O-catalyzed coupling reaction of 4-iodotoluene with 1-dodecanethiol.[a]



Entry	[Cu]	Base	Solvent	Yield [%][b]	Ratio (**3a**/**4a**)[c]
1	Cu_2O	KO*t*Bu	DMSO	26	92:8
2	Cu_2O	KO*t*Bu	DMF	66	79:21
3	Cu_2O	KO*t*Bu	DME	84	–
4	Cu_2O	KO*t*Bu	dioxane	98 (86)	–
5	Cu_2O	KO*t*Bu	dioxane	99 (86)[d]	–
6	Cu_2O	KOEt	dioxane	100 (91)	–
7	Cu_2O	KOMe	dioxane	100 (99)	–
8	Cu_2O	KOH	dioxane	100 (99)	–
9	Cu_2O	NaO*t*Bu	dioxane	13	–
10	Cu_2O	NaOH	dioxane	72	–
11	Cu_2O	K_3PO_4	dioxane	53	–
12	Cu_2O	K_2CO_3	dioxane	53	–
13	Cu_2O	Na_2CO_3	dioxane	26	–
14	Cu_2O	Et_3N	dioxane	2	–
15	CuI	KO*t*Bu	dioxane	82	–
16	CuCl	KO*t*Bu	dioxane	90	–
17	CuO	KO*t*Bu	dioxane	85	–
18	–	KO*t*Bu	dioxane	7	74:26

[a] Reaction conditions unless otherwise stated: Cu_2O (97%, 0.005 mmol, 0.5 mol-%); for CuI, CuCl, and CuO (0.01 mmol, 1.0 mol-%), 4-iodotoluene (1.5 mmol), 1-dodecanethiol (1.0 mmol), base (2.0 mmol), in solvent (0.5 mL). [b] GC yield using tridecane as the internal standard. [c] The ratio was determined by ^1H NMR spectroscopy and GC–MS techniques. [d] Cu_2O (>99.99%) was used. Values in parentheses refer to isolated yields.

As illustrated in Table 2, a number of thiols and aryl iodides were also investigated as coupling partners. Aryl iodides possessing electron-donating or electron-withdrawing groups were successfully coupled to alkyl (Table 2, Entries 1–12) and aryl thiols (Table 2, Entries 13–24) to afford the products in good to excellent yields. 4-Iodoanisole was readily coupled with thiols to give products **3d**, **3e**, **3f**, **3n**, and **3o** in excellent yields. Functional groups including unprotected amines (Table 2, Entries 11, 12, and 19), alcohols (Table 2, Entry 20), halides (Table 2, Entries 21, 24), esters (Table 2, Entry 22), enolizable ketones (Table 2, Entries 23 and 24), and heterocycle-containing moieties (Table 2, Entries 9, 10, 17, and 18) were all tolerated by the reaction conditions employed. Moreover, sterically demanding di-*ortho*-substituted aryl iodides also underwent the cross-coupling reaction to give the desired products (Table 2, Entries 6–8, 15, and 16) in good to excellent yields. We also examined the coupling reactions of some alkyl thiols with aryl iodides under van Koten's conditions[16a] (Table 2, Entries 1–4; results shown in parentheses), and the products were obtained in very low yields. These results suggested that the combination of Cu_2O/KOH in dioxane is a general and efficient system for the copper-catalyzed coupling reaction of aryl iodides with thiols under ligand-free conditions.

Conclusions

We have reported that commercially available Cu_2O powder can be applied as a very reactive catalyst for the coupling reaction of thiols with aryl iodides under ligand-free conditions. There are many advantages to our system: (1) Cu_2O powder is cheap; (2) catalyst loading is as low as 0.5 mol-%, resulting in good to excellent yields and selectivity;[14j] (3) functional groups such as esters, unprotected amines, alcohols, and heterocycles are all tolerated; (4) sterically demanding substrates were also shown to be good coupling partners. Understanding the mechanism of this catalytic system is currently underway in our laboratory.

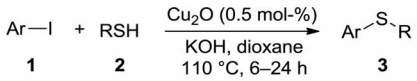
Experimental Section

General Information: All chemicals were purchased from commercial suppliers and were used without further purification. Toluene was dried with sodium; dioxane, DME, DMSO, and DMF were dried with CaH_2 and stored in the presence of activated molecular sieves. All reactions were carried out under an inert atmosphere. Flash chromatography was performed on Merck silica gel 60 (230–400 mesh).

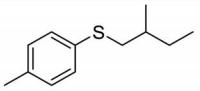
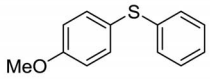
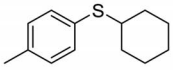
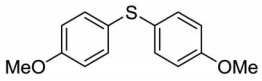
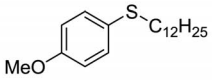
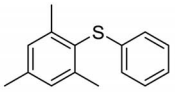
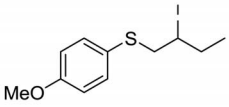
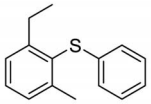
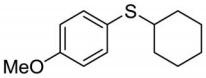
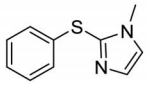
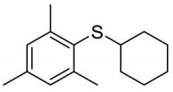
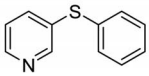
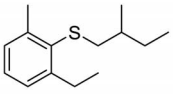
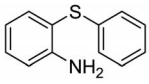
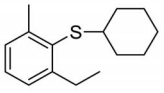
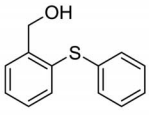
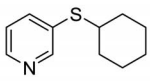
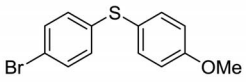
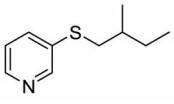
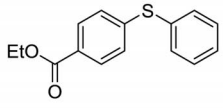
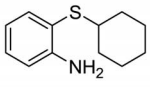
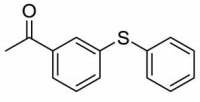
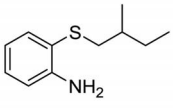
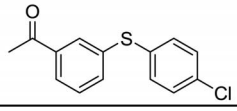
Analysis: NMR spectra were recorded with a Varian Unity Inova-600 or a Varian Mercury-400 instrument by using $CDCl_3$ as the solvent. Chemical shifts are reported in parts per million (ppm) and referenced to the residual solvent resonance. Standard abbreviations indicating multiplicity were used as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, q = quartet, m = multiplet, br. = broad. Melting points were determined by using a Büchi 535 apparatus. GC–MS analyses were performed with an HP 5890 GC equipped with an HP 5972 MS. High-resolution mass spectra were carried out with a Jeol JMS-HX 110 spectrometer by the services at the National Chung Hsing University.

General Procedure for the Cu_2O-Catalyzed Coupling Reaction of 4-Iodotoluene with 1-Dodecanethiol (Table 1): A 4-mL sealable tube equipped with a magnetic stir bar was charged with base (2.0 mmol), Cu_2O (0.7 mg, 0.005 mmol), and 4-iodotoluene (327 mg, 1.5 mmol) in a dry box under a nitrogen atmosphere. The vial was then sealed with a cap containing a PTFE septum and

Table 2. Cu_2O-catalyzed coupling reaction of aryl iodides with thiols.[a]



1 2 3

Entry	Product		Yield [%]	Entry	Product		Yield [%]
1		**3b**	90[b] (38)[c]	13		**3n**	86
2		**3c**	86[b] (27)[c]	14		**3o**	77[e]
3		**3d**	86	15		**3p**	86[f]
4		**3e**	85	16		**3q**	99[f]
5		**3f**	98 (54)[c]	17		**3r**	85[e]
6		**3g**	83[b] (39)[c]	18		**3s**	88[e]
7		**3h**	90	19		**3t**	88[f]
8		**3i**	92[b]	20		**3u**	72[e]
9		**3j**	77	21		**3v**	74[f]
10		**3k**	77	22		**3w**	56[e,g]
11		**3l**	93[d]	23		**3x**	57[e,h]
12		**3m**	91[d]	24		**3y**	51[e,h]

[a] Reaction conditions unless otherwise stated: Cu_2O (0.005 mmol, 0.5 mol-%), aryl iodide (1.2 mmol), thiol (1.0 mmol), KOH (2.0 mmol), in dioxane (0.5 mL), 6 h. [b] 24 h. [c] CuI (0.025 mmol, 2.5 mol-%), aryl iodide (1.0 mmol), thiol (1.3 mmol), K_3PO_4 (1.1 mmol), in NMP (0.19 mL), 100 °C, 16 h; see ref.[16a] for details. [d] Aryl iodide (1.0 mmol), thiol (1.1 mmol). [e] 12 h. [f] 9 h. [g] KOEt as base. [h] DME as solvent.

removed from the dry box. Under a nitrogen atmosphere, solvent (0.5 mL) and 1-dodecanethiol (0.24 mL, 1.0 mmol) were added by syringe, and the reaction vessel was heated at 110 °C in an oil bath. After stirring at this temperature for 6 h, the heterogeneous mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The resulting solution was directly filtered through a pad of Celite then washed with ethyl acetate (20 mL) and concentrated to give the crude material, which was then purified by column chromatography (SiO_2, hexane and CH_2Cl_2 or EtOAc) to yield **3a**.

Dodecyl *p*-Tolyl Sulfide (3a): Following the above general procedure and using KOH (112.0 mg, 2.0 mmol), 1-dodecanethiol (0.24 mL, 1.0 mmol), 4-iodotoluene (327.0 mg, 1.5 mmol). Purification (SiO_2, hexane) provided **3a** (Table 1, Entry 8)[21] as a colorless oil (288 mg, 99% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 6.8 Hz, 3 H), 1.23–1.63 (m, 20 H), 2.30 (s, 3 H), 2.85 (t, J = 7.2 Hz, 2 H), 7.07 (d, J = 8.4 Hz, 2 H), 7.22 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 21.0, 22.7, 28.8, 29.16, 29.24, 29.3, 29.5, 29.57, 29.63, 31.9, 34.4, 129.6, 129.8, 133.2, 135.8 ppm.

General Procedure for the Cu_2O-Catalyzed Coupling Reaction of Aryl Iodides with Thiols (Table 2): A 4-mL sealable tube equipped with a magnetic stir bar was charged with KOH (112.0 mg, 2.0 mmol) or KOEt (168.0 mg, 2.0 mmol), Cu_2O (0.7 mg, 0.005 mmol), and aryl iodide (1.2 mmol) in a dry box under a nitrogen atmosphere. The vial was then sealed with a cap containing a PTFE septum and removed from the dry box. Under a nitrogen atmosphere, dioxane or DME (0.5 mL) and 1-dodecanethiol (0.24 mL, 1.0 mmol) were added by syringe, and the reaction vessel was heated at 110 °C in an oil bath. After stirring at this temperature for 6–24 h, the heterogeneous mixture was cooled to room temperature and diluted with ethyl acetate (20 mL). The resulting solution was directly filtered through a pad of Celite and then washed with ethyl acetate (20 mL) and concentrated to give the crude material, which was then purified by column chromatography (SiO_2, hexane and CH_2Cl_2 or EtOAc) to give **3**.

(2-Methylbutyl)(*p*-tolyl)sulfane (3b): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 2-methylbutane-1-thiol (0.125 mL, 1.0 mmol), and 4-iodotoluene (262.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3b** (174 mg, 90% yield) as a colorless oil (Table 2, Entry 1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 4.8 Hz, 3 H), 1.00 (d, J = 6.8 Hz, 3 H), 1.19–1.27 (m, 1 H), 1.47–1.64 (m, 2 H), 2.29 (s, 3 H), 2.70 (dd, J = 7.2, 12.4 Hz, 1 H), 2.89 (dd, J = 7.2, 12.4 Hz, 1 H), 7.06 (d, J = 6.4 Hz, 2 H), 7.23 (d, J = 6.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.2, 18.8, 20.9, 28.7, 34.4, 41.4, 129.5, 129.6, 133.6, 135.5 ppm. HRMS (EI): calcd. for $C_{12}H_{18}S$ 194.1129; found 194.1131.

Cyclohexyl(*p*-tolyl)sulfane (3c): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), cyclohexanethiol (0.125 mL, 1.0 mmol), and 4-iodotoluene (262.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3c** (177 mg, 86% yield) as a colorless oil (Table 2, Entry 2).[9c] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.18–2.01 (m, 10 H), 2.31 (s, 3 H), 2.98–3.04 (m, 1 H), 7.09 (d, J = 9.2 Hz, 2 H), 7.31 (d, J = 9.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 25.7, 26.0, 33.3, 47.0, 129.5, 131.1, 132.7, 136.8 ppm.

Dodecyl(4-methoxyphenyl)sulfane (3d): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 1-dodecanethiol (0.24 mL, 1.0 mmol), and 4-iodoanisole (281.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3d** (270 mg, 86% yield) as a colorless solid (Table 2, Entry 3).[22] M.p. 44–45 °C (ref.[22] 44–45 °C) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 3 H), 1.25–1.40 (m, 18 H), 1.57 (m, 2 H), 2.81 (t, J = 7.6 Hz, 2 H), 3.80 (s, 3 H), 6.84 (d, J = 8.4 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.6, 28.6, 29.1, 29.3, 29.46, 29.53, 29.58, 29.6, 31.9, 35.7, 55.1, 114.4, 127.0, 132.8, 158.6 ppm.

4(4-Methoxyphenyl)(2-methylbutyl)sulfane (3e): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 2-methylbutane-1-thiol (0.125 mL, 1.0 mmol), and 4-iodoanisole (281.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3e** (178 mg, 85% yield) as a colorless oil (Table 2 Entry 4). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, J = 5.2 Hz, 3 H), 0.98 (d, J = 6.8 Hz, 3 H), 1.19–1.26 (m, 1 H), 1.47–1.60 (m, 2 H), 2.65 (dd, J = 7.6, 12.4 Hz, 1 H), 2.84 (dd, J = 7.6, 12.4 Hz, 1 H), 3.76 (s, 3 H), 6.82 (d, J = 5.2 Hz, 2 H), 7.32 (d, J = 5.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 18.6, 28.5, 34.3, 42.8, 55.0, 114.3, 127.4, 132.4, 158.4 ppm. HRMS (EI): calcd. for $C_{12}H_{18}OS$ 210.1078; found 210.1072.

Cyclohexyl(4-methoxyphenyl)sulfane (3f): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), cyclohexanethiol (0.123 mL, 1.0 mmol), and 4-iodoanisole (281.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3f** (218 mg, 98% yield) as a colorless oil (Table 2, Entry 5).[14a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.21–1.93 (m, 10 H), 2.88–2.91 (m, 1 H), 3.76 (s, 3 H), 6.82 (d, J = 9.6 Hz, 2 H), 7.37 (d, J = 9.6 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 25.9, 33.2, 47.7, 55.1, 114.1, 124.8, 135.4, 159.1 ppm.

Cyclohexyl(mesityl)sulfane (3g): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), cyclohexanethiol (0.123 mL, 1.0 mmol), and 2-iodo-1,3,5-trimethylbenzene (295.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3g** (194 mg, 83% yield) as a colorless oil (Table 2, Entry 6). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.85 (m, 10 H), 2.24 (s, 3 H), 2.49 (s, 6 H), 2.74–2.80 (m, 1 H), 6.90 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 22.2, 25.8, 26.2, 33.6, 47.3, 128.7, 129.6, 137.6, 143.1 ppm. HRMS (EI): calcd. for $C_{15}H_{22}S$ 234.1442; found 234.1441.

(2-Ethyl-6-methylphenyl)(2-methylbutyl)sulfane (3h): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 2-methylbutane-1-thiol (0.125 mL, 1.0 mmol), and 1-ethyl-2-iodo-3-methylbenzene (295.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3h** (200 mg, 90% yield) as a colorless oil (Table 2, Entry 7). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.2 Hz, 3 H), 1.02 (d, J = 8.8 Hz, 3 H), 1.20–1.27 (m, 4 H), 1.49–1.61 (m, 2 H), 2.50 (dd, J = 8.4, 14.0 Hz, 1 H), 2.59 (s, 3 H), 2.64 (dd, J = 8.4, 14.0 Hz, 1 H), 2.95–3.01 (m, 2 H), 7.08–7.16 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.3, 16.1, 19.0, 22.0, 28.2, 28.8, 35.3, 43.5, 126.4, 128.0, 128.1, 134.1, 143.0, 148.7 ppm. HRMS (EI): calcd. for $C_{14}H_{22}S$ 222.1442; found 222.1435.

Cyclohexyl(2-ethyl-6-methylphenyl)sulfane (3i): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), cyclohexanethiol (0.123 mL, 1.0 mmol), and 1-ethyl-2-iodo-3-methylbenzene (295.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3i** (216 mg, 92% yield) as a colorless oil (Table 2, Entry 8). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.85 (m, 13 H), 2.55 (s, 3 H), 2.75–2.83 (m, 1 H), 2.97 (m, 2 H), 7.13 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.9, 22.4, 25.8, 26.2, 28.2, 33.6, 47.9, 126.3, 127.9, 128.1, 132.4, 143.5, 149.3 ppm. HRMS (EI): calcd. for $C_{15}H_{22}S$ 234.1442; found 234.1446.

3-(Cyclohexylthio)pyridine (3j): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), cyclohexanethiol (0.123 mL, 1.0 mmol), and 3-iodopyridine (245.0 mg, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 6:1) provided **3j** (148 mg, 77% yield) as a colorless oil (Table 2, Entry 9). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23–2.05 (m, 10 H), 3.08–3.13 (m, 1 H), 7.21–7.26 (m, 1 H), 7.70–7.73 (m, 1 H), 8.46–8.48 (m, 1 H), 8.64 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 25.6, 32.9, 46.4, 123.2, 131.9, 139.2, 147.3, 152.2 ppm. HRMS (EI): calcd. for $C_{11}H_{15}NS$ 193.0925; found 193.0920.

3-(2-Methylbutylthio)pyridine (3k): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 2-methylbutane-1-thiol (0.125 mL, 1.0 mmol), and 3-iodopyridine (245.0 mg, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 6:1) provided **3k** (140 mg, 77% yield) as a colorless oil (Table 2, Entry 10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 5.2 Hz, 3 H), 1.00 (d, J = 7.6 Hz, 3 H), 1.26–1.30 (m, 1 H), 1.49–1.6 (m, 2 H), 2.74 (dd, J = 6.4, 13.6 Hz, 1 H), 2.91 (dd, J = 6.4, 13.6 Hz, 1 H), 7.15–7.20 (m, 1 H), 7.58–7.63 (m, 1 H), 8.37–8.39 (m, 1 H), 8.55 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.0, 18.5, 28.4, 34.2, 40.5, 123.2, 134.4, 136.2, 146.4, 149.5 ppm. HRMS (EI): calcd. for $C_{10}H_{15}NS$ 181.0920; found 181.0928.

2-(Cyclohexylthio)aniline (3l): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), cyclohexanethiol (0.135 mL, 1.1 mmol), and 2-iodoaniline (219.0 mg, 1.0 mmol). Purification

(SiO_2; hexane/EtOAc, 20:1) provided **3l** (193 mg, 93% yield) as a green oil (Table 2, Entry 11). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19–2.02 (m, 10 H), 2.88–2.98 (m, 1 H), 4.41 (s, 2 H), 6.66–6.78 (m, 2 H), 7.10–7.18 (m, 1 H), 7.36–7.42 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.0, 26.4, 33.9, 47.2, 115.1, 117.2, 118.5, 130.1, 137.6, 149.2 ppm. HRMS (EI): calcd. for $C_{12}H_{17}NS$ 207.1082; found 207.1089.

2-(2-Methylbutylthio)aniline (3m): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 2-methylbutane-1-thiol (0.137 mL, 1.1 mmol), and 2-iodoaniline (219.0 mg, 1.0 mmol). Purification (SiO_2; hexane/EtOAc, 20:1) provided **3m** (177 mg, 91% yield) as a brown oil (Table 2, Entry 12). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.84 (t, J = 8.8 Hz, 3 H), 0.98 (d, J = 9.2 Hz, 3 H), 1.17–1.24 (m, 1 H), 1.46–1.57 (m, 2 H), 2.57 (dd, J = 7.2, 12.4 Hz, 1 H), 2.74 (dd, J = 7.2, 12.4 Hz, 1 H), 4.31 (s, 2 H), 6.64–6.88 (m, 2 H), 7.04–7.09 (m, 1 H), 7.34–7.36 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.1, 18.6, 28.4, 34.6, 41.9, 114.7, 118.4, 118.8, 129.1, 135.1, 147.7 ppm. HRMS (EI): calcd. for $C_{11}H_{17}NS$ 195.1082; found 195.1074.

4-Methoxyphenyl Phenyl Sulfide (3n): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), thiophenol (0.10 mL, 1.0 mmol), and 4-iodoanisole (281.0 mg, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 10:1) provided **3n** (184 mg, 86% yield) as a colorless oil (Table 2, Entry 13).[9c] ^1H NMR (400 MHz, $CDCl_3$): δ = 3.83 (s, 3 H), 6.89 (d, J = 8.8 Hz, 2 H), 7.09–7.26 (m, 5 H), 7.41 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 114.9, 124.3, 125.7, 128.2, 128.9, 135.3, 138.6, 159.8 ppm.

4-Methylphenyl 4-Methoxyphenyl Sulfide (3o): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 4-methoxythiophenol (0.125 mL, 1.00 mmol), and 4-iodoanisole (281.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3o** (189 mg, 77% yield) as a white solid (Table 2, Entry 14).[9c] ^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 6 H), 6.83 (d, J = 8.8 Hz, 4 H), 7.27 (d, J = 8.8 Hz, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 114.7, 127.4, 132.7, 158.9 ppm.

Mesityl Phenyl Sulfide (3p): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), thiophenol (0.10 mL, 1.0 mmol), and 2-iodo-1,3,5-trimethylbenzene (295.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3p** (195 mg, 86% yield) as a colorless oil (Table 2, Entry 15).[13] ^1H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3 H), 2.38 (s, 6 H), 6.90–6.92 (m, 2 H), 7.01 (s, 2 H), 7.02–7.07 (m, 1 H), 7.15–7.19 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 21.6, 124.4, 125.4, 126.9, 128.8, 129.3, 138.3, 139.1, 143.6 ppm.

2-Ethyl-6-methylphenyl Phenyl Sulfide (3q): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), thiophenol (0.10 mL, 1.0 mmol), 2-ethyl-6-methyliodobenzene (295.0 mg, 1.2 mmol). Purification (SiO_2, hexane) provided **3q** (227 mg, 99% yield)as a colorless oil (Table 2, Entry 16). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.17 (t, J = 7.6 Hz, 3 H), 2.39 (s, 3 H), 2.86 (q, J = 7.6 Hz, 2 H), 6.90–6.92 (m, 2 H), 7.03–7.07 (m, 1 H), 7.15–7.21 (m, 4 H), 7.25–7.30 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.8, 21.8, 28.4, 124.5, 125.5, 127.0, 128.5, 128.8, 129.5, 129.7, 138.6, 144.0, 149.7 ppm. HRMS (EI): calcd. for $C_{15}H_{16}S$ 228.0973; found 228.0979.

2-(Phenylsulfanyl)-*N*-methylimidazole (3r): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 2-mercapto-1-methylimidazole (114.0 mg, 1.0 mmol), and iodobenzene (0.13 mL, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 2:1) provided **3r** (161 mg, 85% yield) as a yellow oil (Table 2, Entry 17).[11b] ^1H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3 H), 7.11 (d, J = 1.2 Hz, 1 H), 7.22–7.30 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 33.6, 123.8, 126.3, 127.7, 129.1, 129.8, 134.7, 137.6 ppm.

3-Pyridyl Phenyl Sulfide (3s): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), thiophenol (0.10 mL, 1.0 mmol), and 3-iodopyridine (246.0 mg, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 9:1) provided **3s** (165 mg, 88% yield) as a yellow oil (Table 2, Entry 18).[23] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.11–7.14 (m, 1 H), 7.15–7.33 (m, 5 H), 7.51–7.54 (m, 1 H), 8.38–8.41 (m, 1 H), 8.52 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 123.7, 127.6, 129.2, 131.5, 133.4, 133.7, 137.6, 147.7, 150.8 ppm.

2-Phenylsulfanylaniline (3t): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), thiophenol (0.10 mL, 1.0 mmol), and 2-iodoaniline (263.0 mg, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 9:1) provided **3t** (176 mg, 88% yield) as a yellow oil (Table 2, Entry 19).[24] ^1H NMR (400 MHz, $CDCl_3$): δ = 4.28 (br. s, 2 H), 6.74–6.80 (m, 2 H), 7.07–7.13 (m, 3 H), 7.20–7.25 (m, 3 H), 7.45–7.47 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 114.2, 115.3, 118.7, 125.3, 126.4, 128.9, 131.1, 136.8, 137.4, 148.8 ppm.

[2-(Phenylthio)phenyl]methanol (3u): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), thiophenol (0.10 mL, 1.0 mmol), and 2-iodobenzyl alcohol (281.0 mg, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 9:1) provided **3u** (155 mg, 72% yield) as a colorless oil (Table 2, Entry 20).[13] ^1H NMR (400 MHz, $CDCl_3$): δ = 2.69 (br. s, 1 H), 4.71 (s, 2 H), 7.13–7.23 (m, 6 H), 7.26–7.33 (m, 2 H), 7.45 (d, J = 7.2 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.1, 126.4, 128.20, 128.23, 128.3, 129.1, 129.3, 132.1, 133.7, 135.9, 142.2 ppm.

4-Bromophenyl 4-Methoxyphenyl Sulfide (3v): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 4-methoxythiophenol (0.125 mL, 1.0 mmol), and 1-bromo-4-iodobenzene (338.0 mg, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 9:1) provided **3v** (218 mg, 74% yield) as a yellow oil (Table 2, Entry 21).[21] ^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 6.90 (d, J = 8.4 Hz, 2 H), 7.07 (d, J = 8.4 Hz, 2 H), 7.18 (d, J = 8.8 Hz, 2 H), 7.40 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 115.1, 123.7, 128.9, 129.2, 131.5, 135.4, 137.3, 160.0 ppm.

Ethyl 4-Phenylsulfanylbenzoate (3w): Following the general procedure and using KOEt (168.0 mg, 2.0 mmol), thiophenol (0.10 mL, 1.0 mmol), and ethyl-4-iodobenzoate (0.2 mL, 1.2 mmol). Purification (SiO_2; hexane/EtOAc, 9:1) provided **3w** (144 mg, 56% yield) as a colorless oil (Table 2, Entry 22).[13] ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 7.2 Hz, 3 H), 4.33 (q, J = 7.2 Hz, 2 H), 7.19 (d, J = 8.8 Hz, 2 H), 7.34–7.39 (m, 3 H), 7.44–7.48 (m, 2 H), 7.88 (d, J = 8.8 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 60.8, 127.6, 127.8, 128.4, 129.5, 130.0, 132.5, 133.5, 144.0, 166.1 ppm.

1-[3-(Phenylthio)phenyl]ethanone (3x): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), thiophenol (0.10 mL, 1.0 mmol), 3′-iodoacetophenone (0.17 mL, 1.2 mmol), and DME (0.5 mL). Purification (SiO_2; hexane/EtOAc, 9:1) provided **3x** (130 mg, 57% yield) as a yellow oil (Table 2, Entry 23).[14k] ^1H NMR (400 MHz, $CDCl_3$): δ = 2.52 (s, 3 H), 7.26–7.37 (m, 6 H), 7.41–7.44 (m, 1 H), 7.75–7.77 (m, 1 H), 7.76–7.77 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 126.3, 127.4, 129.1, 129.2, 129.6, 131.5, 134.2, 134.3, 137.3, 137.6, 197.0 ppm.

1-[3-(4-Chlorophenylthio)phenyl]ethanone (3y): Following the general procedure and using KOH (112.0 mg, 2.0 mmol), 4-chlorothiophenol (173.0 mg, 1.0 mmol), 3′-iodoacetophenone (0.17 mL, 1.2 mmol), and DME (0.5 mL). Purification (SiO_2; hexane/EtOAc, 9:1) provided **3y** (133 mg, 51% yield) as a yellow oil (Table 2, En-

try 24). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.56 (s, 3 H), 7.26–7.37 (m, 4 H), 7.39–7.41 (m, 1 H), 7.45–7.47 (m, 1 H), 7.81 (dt, J = 7.6, 1.6 Hz, 1 H), 7.90 (t, J = 1.6 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.6, 126.9, 129.3, 129.5, 130.2, 132.8, 133.2, 133.8, 134.8, 136.8, 138.0, 197.2 ppm. HRMS (EI) calcd. for $C_{14}H_{11}OSCl$ 262.0219; found 262.0211.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra for new compounds.

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