Microwave-Assisted Efficient Synthesis of Aryl Thioethers through C–H Functionalization of Arenes

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Abstract: Microwave-assisted iridium-catalyzed *meta* C–H borylation followed by copper-promoted C–S bond coupling reactions in one pot is reported. This approach enables the syntheses of aryl thioethers in short reaction times (within 2.5 hours). The system shows good functional-group compatibility, as chloro, trifluoromethyl, fluoro, and pyridine groups are tolerated by the reaction conditions. Both aryl and alkyl thiols are coupled smoothly. The products were formed with excellent regioselectivity in *meta* position.

Key words: microwave, aryl thioether, iridium, copper, C–H functionalization, arene

From an atom-economy point of view, transition-metal-catalyzed C–H functionalization[1] is an attractive strategy for constructing carbon–carbon[2] and carbon–heteroatom bonds.[3,4] Compared with C–C, C–O, and C–N bond formations, the C–S bond-coupling reaction through C–H activation is relatively less studied because of the strong binding affinity between the sulfur moiety and transition metals which might inhibit the activity of the metals.[5–9] 2-Phenylpyridine has been described to form C–S bonds with high *ortho* regioselectivity through copper[5] or palladium[6] catalysis. Notably, pyridine has played an important role as a directing group in these two protocols.[5,6] The copper-[7] and palladium-catalyzed[8] C–S bond formation via C–H activation without directing group has been reported. However, some limitations remain with these systems.[7,8] First, these systems need electron-rich arenes as the starting materials. Second, the systems produce *ortho* and *para* products, moreover, the mixtures of *ortho*- and *para*-arylthiolated products were formed at the same time in most cases. Interestingly, Frost et al. reported the first ruthenium-catalyzed *meta* sulfonation of 2-phenylpyridines, however, pyridine is necessary as a directing group.[9] Aryl thioethers are important motifs in pharmaceuticals.[10] Many methods have been reported for preparing aryl thioethers.[11–20] We have recently reported the one-pot *meta* C–H thioetherification of arenes without a directing group[21] through iridium-catalyzed C–H borylation[22] followed by copper-catalyzed C–S bond formation.[23] In general, it requires 48 hours for this two-step process. Microwave irradiation has been widely applied to organic synthesis due to the high efficiency of this technique.[24–27] Herein, we report the microwave-assisted (1) iridium-catalyzed C–H borylation[27] and (2) copper-catalyzed C–S bond-forming process.

As illustrated in Table 1, *m*-chlorotoluene (**1a**) was treated with pin_2B_2 under microwave-promoted iridium-catalyzed borylation,[27] after removal of the volatile components, the resulting arylboronate was then conducted with thiophenol in the presence of 1.5 equivalents of $Cu(OAc)_2$ and 3 equivalents of pyridine in methyl *tert*-butyl ether (MTBE), the reaction was subjected to microwave irradiation for 1.5 hours at 135 °C (without further optimization) to give the product **2a** with a 60% yield in one pot (Table 1, entry 1).[28] Other arenes were sequentially reacted with pin_2B_2 under iridium-catalyzed borylation, followed by copper-promoted C–S coupling reaction with aryl thiols. Aryl thiols bearing electron-donating or electron-withdrawing groups such as methoxy, trifluoromethyl, chloro, and fluoro in the benzene rings are suitable as the coupling partners. Notable, this system shows good functional-group tolerance, chloro, trifluoromethyl, and fluoro groups are all tolerated under the reaction conditions. The products were obtained with high *meta* regioselectivity in all cases, this two-step process takes a short reaction time of 2.5 hours.

It is known that the alkyl thiols are less reactive for the coupling with arylboronates,[21] therefore we turned our attention to alkyl thiols for this one-pot reaction. To our delight, the products were formed in good to excellent yields. The results are summarized in Table 2, alkyl thiols such as dodecanethiol (Table 2, entries 1, 4, 8, 11, and 15), 2-methy-1-butanethiol (Table 2, entries 2, 5, 9, and 12), cyclohexanethiol (Table 2, entries 3, 6, 10, and 13), benzyl mercaptan (Table 2, entries 7 and 14) are coupled with a variety of starting arenes, giving aryl alkyl thioethers in moderate to good yields. Notably, this operation takes only 2.5 hours for two steps in one pot. Furthermore, functional groups including chloro, trifluoromethyl, and pyridine are stable during the catalysis.

In conclusion, we have developed a convenient protocol to access diaryl and aryl alkyl thioethers under microwave-promoted sequential iridium-catalyzed borylation and copper-promoted C–S bond-forming reaction from simple arenes in one pot. This two-step process takes only 2.5 hours to give the corresponding thioethers in good to excellent yields with excellent *meta* regioselectivity. This system shows good functional-group tolerance; chloro, trifluoromethyl, fluoro, and pyridine are all tolerated by the reaction conditions employed.

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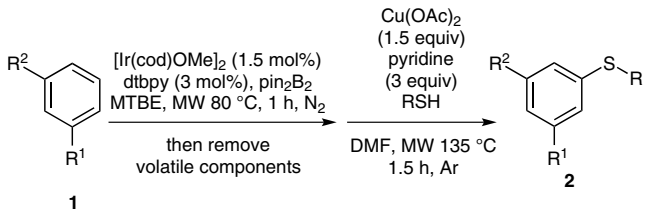
Table 1 Microwave-Promoted Tandem Iridium-Catalyzed Borylation and Copper-Promoted Coupling with Aryl Thiols[a]



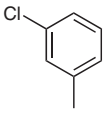
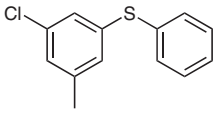
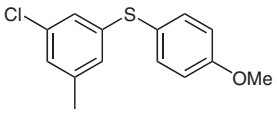
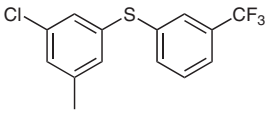
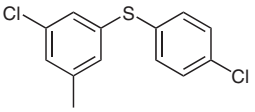
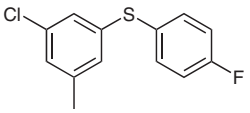
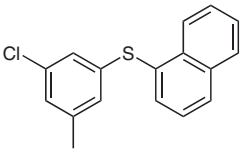
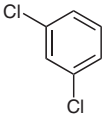
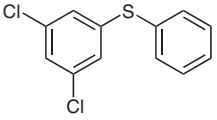
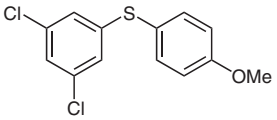
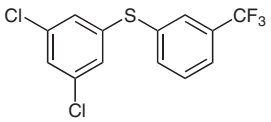
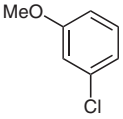
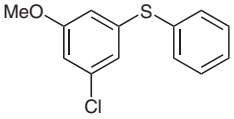
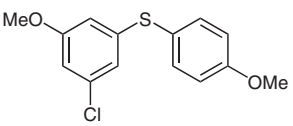
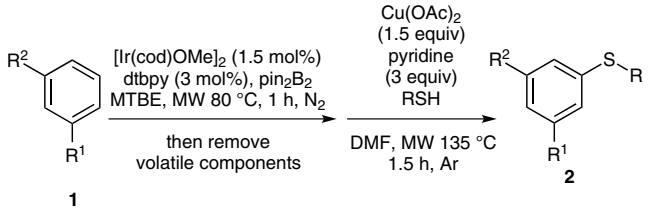
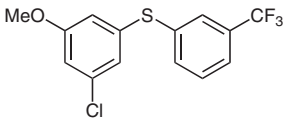
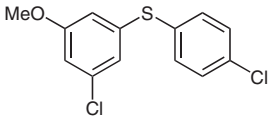
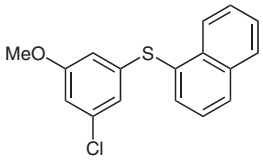
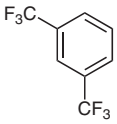
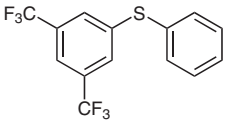
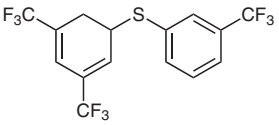
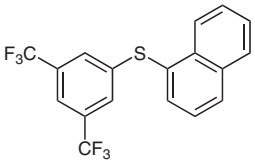
Entry	1	Product	Yield (%)
1	**1a** 	**2a** 	60
2	**1a**	**2b** 	47
3	**1a**	**2c** 	78
4	**1a**	**2d** 	60
5	**1a**	**2e** 	50
6	**1a**	**2f** 	50
7	**1b** 	**2g** 	61
8	**1b**	**2h** 	46
9	**1b**	**2i** 	62
10	**1c** 	**2j** 	68
11	**1c**	**2k** 	53

Table 1 Microwave-Promoted Tandem Iridium-Catalyzed Borylation and Copper-Promoted Coupling with Aryl Thiols[a] (continued)



1 **2**

Entry	**1**	Product	Yield (%)
12	**1c**	**2l** 	46
13	**1c**	**2m** 	50
14	**1c**	**2n** 	65
15	**1d** 	**2o** 	70
16	**1d**	**2p** 	70
17	**1d**	**2q** 	63

[a] Reaction conditions unless otherwise stated: arene (1.0 mmol), $[Ir(cod)OMe]_2$ (0.015 mol, 1.5 mol%), dtbpy (0.03 mmol, 3.0 mol%) in MTBE (2.0 mL) for the first step; $Cu(OAc)_2$ (0.75 mmol, 1.5 equiv), pyridine (1.5 mmol, 3 equiv), aryl thiol (0.5 mmol) in DMF (2 mL) under argon atmosphere for the second step.

Table 2 Microwave-Assisted Sequential Iridium-Catalyzed Borylation and Copper-Promoted Coupling with Alkyl Thiols[a]

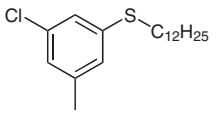
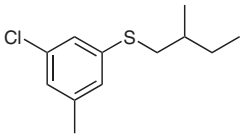
Entry	**1**	Product	Yield (%)
1	**1a**	**3a** 	90
2	**1a**	**3b** 	68

Table 2 Microwave-Assisted Sequential Iridium-Catalyzed Borylation and Copper-Promoted Coupling with Alkyl Thiols[a] (continued)

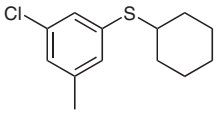
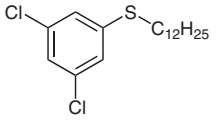
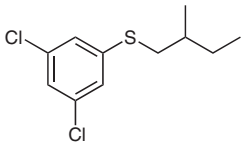
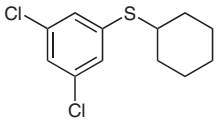
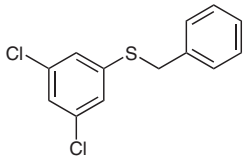
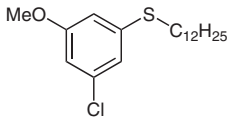
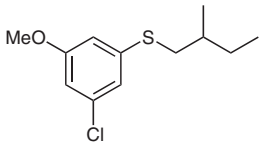
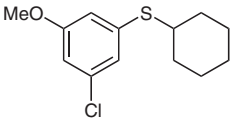
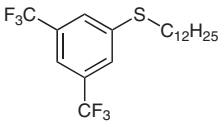
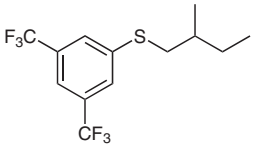
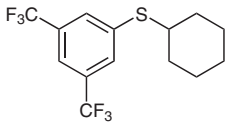
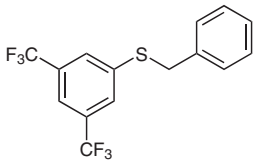
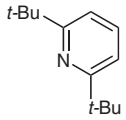
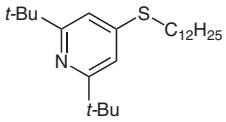
Entry	1	Product	Yield (%)
3	**1a**	**3c** 	91
4	**1b**	**3d** 	75
5	**1b**	**3e** 	83
6	**1b**	**3f** 	85
7	**1b**	**3g** 	55
8	**1c**	**3h** 	78
9	**1c**	**3i** 	65
10	**1c**	**3j** 	71
11	**1d**	**3k** 	60
12	**1d**	**3l** 	57
13	**1d**	**3m** 	55

Table 2 Microwave-Assisted Sequential Iridium-Catalyzed Borylation and Copper-Promoted Coupling with Alkyl Thiols[a] (continued)

Entry	1	Product	Yield (%)
14	**1d**	**3n** 	66
15	**1e** 	**3o** 	45

[a] Reaction conditions unless otherwise stated: arene (1.0 mmol), $[Ir(cod)OMe]_2$ (0.015 mol, 1.5 mol%), dtbpy (0.03 mmol, 3.0 mol%) in MTBE (2.0 mL) for the first step; $Cu(OAc)_2$ (0.75 mmol, 1.25 equiv), pyridine (1.5 mmol, 2.5 equiv), alkyl thiol (0.5 mmol) in DMF (2 mL) under argon atmosphere for the second step.

Acknowledgment

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

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(28) **General Procedure for the Synthesis of Compounds 2a–q**

A flask equipped with a magnetic stirrer bar was charged with $[Ir(cod)OMe)]_2$ (99.0 mg, 0.015 mmol), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (82.0 mg, 0.03 mmol) and pin_2B_2 (254 mg, 1.0 mmol) in a nitrogen-filled glove box. This flask was then covered with a rubber septum and removed from the glove box. Under a nitrogen atmosphere, arene (1.0 mmol) and MTBE (2.0 mL) were added via syringe, and the reaction vessel was placed under microwave irradiation at 80 °C. After stirring at this temperature for 1 h, the heterogeneous mixture was cooled to r.t., after removal of the volatile components under vacuum. The flask was returned to the glove box, $Cu(OAc)_2$ (136 mg, 0.75 mmol) was added, the flask was then covered with a rubber septum and removed from the glove box. Under an argon atmosphere, aryl thiol (0.5 mmol), pyridine (0.123 mL, 1.5 mmol), and DMF (2.0 mL) were added via syringe, and the reaction vessel was placed under microwave irradiation at 135 °C. After stirring at this temperature for 1.5 h, the heterogeneous mixture was cooled to r.t. and diluted with EtOAc (20 mL). The resulting solution was directly filtered through a pad of silica gel then washed with EtOAc (20 mL) and concentrated to give the crude material which was then purified by column chromatography (SiO_2, hexane) to yield **2**.

Data for some representative examples are shown here.

3-Chloro-5-methylphenyl Phenyl Sulfide (2a)[21a]

Following the general procedure, using $[Ir(cod)OMe]_2$ (99.0 mg, 0.015 mmol), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (82.0 mg, 0.03 mmol), pin_2B_2 (254 mg, 1.0 mmol), and 3-chlorotoluene (0.123 mL, 1.0 mmol) in MTBE (2.0 mL) for the first step. After removal of the volatile components under vacuum, $Cu(OAc)_2$ (136 mg, 0.75 mmol), thiophenol (0.053 mL, 0.5 mmol), and DMF (2.0 mL) were used, then purified by column chromatography (SiO_2, hexane) to provide **2a** as a colorless oil (70.0 mg, 60% yield). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 3 H), 6.97–7.04 (m, 3 H), 7,25–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.0, 126.6, 127.5, 127.7, 128.7, 129.3, 132.0, 134.1, 134.4, 138.0, 140.4 ppm.

3-Chloro-5-methylphenyl 4-Methoxyphenyl Sulfide (2b)[21a]

Following the general procedure, using $[Ir(cod)OMe)]_2$ (99.0 mg, 0.015 mmol), 4,4′-di-*tert*-butyl-2,2′-dipyridyl

(82.0 mg, 0.03 mmol), pin_2B_2 (254 mg, 1.0 mmol), and 3-chlorotoluene (0.123 mL, 1.0 mmol) in MTBE (2.0 mL) for the first step. After removal of the volatile components under vacuum, $Cu(OAc)_2$ (136 mg, 0.75 mmol), 4-methoxythiophenol (0.063 mL, 0.5 mmol), and DMF (2.0 mL) were used, then purified by column chromatography (SiO_2, hexane) to provide **2b** as a colorless oil (62.0 mg, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.20 (s, 3 H), 3.78 (s, 3 H), 6.82–6.90 (m, 5 H), 7.39–7.41 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 55.2, 115.0, 122.7, 124.0, 126.1, 126.3, 134.3, 136.0, 140.1, 140.7, 160.1 ppm.

3-Chloro-5-methylphenyl 3-Trifluoromethyl Phenyl Sulfide (2c)

Following the general procedure, using $[Ir(cod)OMe]_2$ (99.0 mg, 0.015 mmol), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (82.0 mg, 0.03 mmol), pin_2B_2 (254 mg, 1.0 mmol), and 3-chlorotoluene (0.123 mL, 1.0 mmol) in MTBE (2.0 mL) for the first step. After removal of the volatile components under vacuum, $Cu(OAc)_2$ (136 mg, 0.75 mmol), 3-trifluoromethylthiophenol (0.070 mL, 0.5 mmol), and DMF (2.0 mL) were used, then purified by column chromatography (SiO_2, hexane) to provide **2c** as a colorless oil (118.0 mg, 78% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.29 (s, 3 H), 7.08 (d, *J* = 7.6 Hz, 2 H), 7.14 (s, 1 H), 7.40–7.49 (m, 3 H), 7.58 (s, 1 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 123.6 (q, *J* = 271.1 Hz), 123.9 (q, *J* = 3.7 Hz), 127.1 (q, *J* = 3.9 Hz) 128.3, 128.8, 129.7, 130.3, 131.6 (q, *J* = 32.4 Hz), 133.7, 134.8, 135.6, 136.9, 141.0 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –64.4 (s) ppm. HRMS (EI): *m/z* calcd for $C_{14}H_{10}F_3ClS$: 302.0144; found: 302.0148.

3-Chloro-5-methylphenyl 4-Chlorophenyl Sulfide (2d)[21a]

Following the general procedure, using $[Ir(cod)OMe]_2$ (99.0 mg, 0.015 mmol), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (82.0 mg, 0.03 mmol), pin_2B_2 (254 mg, 1.0 mmol), and 3-chlorotoluene (0.123 mL, 1.0 mmol) in MTBE (2.0 mL) for the first step. After removal of the volatile components under vacuum, $Cu(OAc)_2$ (136 mg, 0.75 mmol), 4-chlorothiophenol (74 mg, 0.5 mmol), and DMF (2.0 mL) were used, then purified by column chromatography (SiO_2, hexane) to provide **2d** as a colorless oil (0.081 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3 H), 6.98 (s, 1 H), 7.03 (s, 1 H), 7.05 (s, 1 H), 7.29 (s, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 127.0, 128.0, 129.1, 129.5, 133.0, 133.1, 133.8, 134.6, 137.3, 140.7 ppm.

3-Chloro-5-methylphenyl 4-Fluorophenyl Sulfide (2e)[21b]

Following the general procedure, using $[Ir(cod)OMe]_2$ (99.0 mg, 0.015 mmol), 4,4′-di-*tert*-butyl-2,2′-dipyridyl (82.0 mg, 0.03 mmol), pin_2B_2 (254 mg, 1.0 mmol), and 3-chlorotoluene (0.123 mL, 1.0 mmol) in MTBE (2.0 mL) for the first step. After removal of the volatile components under vacuum, $Cu(OAc)_2$ (0.1362 g, 0.75 mmol), 4-fluorothiophenol (0.055 mL, 0.5 mmol), and DMF (2.0 mL) were used, then purified by column chromatography (SiO_2, hexane) to provide **2e** as a colorless oil (63.0 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.26 (s, 3 H), 6.91 (s, 1 H), 6.95 (s, 1 H), 6.98 (s, 1 H), 7.03–7.08 (m, 2 H), 7.40–7.43 (m, 2 H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.1, 116.6, 116.7, 125.7, 127.3, 127.8, 128.7, 128.7, 134.6, 135.0, 135.0, 138.8, 140.5, 161.9, 163.6 ppm. ^{19}F NMR (376 MHz, $CDCl_3$): δ = –114.3 (s) ppm.

