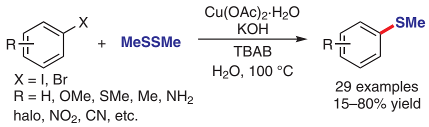
Copper-Catalyzed Methylthiolation of Aryl Iodides and Bromides with Dimethyl Disulfide in Water

Ying-yu Wang
Xiang-mei Wu*
Ming-hua Yang

Department of Chemistry, Lishui University,
Lishui, Zhejiang 323000, P. R. of China
lswxm7162@163.com
mhyang@lsu.edu.cn



Received: 06.02.2020
Accepted after revision: 23.04.2020
Published online: 02.07.2020
DOI: 10.1055/s-0040-1707131; Art ID: st-2020-u0076-l

Abstract An efficient route to aryl methyl sulfides through the copper-catalyzed coupling reaction of aryl iodides or bromides with dimethyl disulfide in water is described. Electron-donating and electron-withdrawing functional groups in the substrates were tolerated, and the corresponding products were obtained in moderate to good yields.

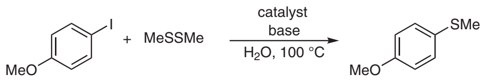
Key words methylthiolation, aryl halides, dimethyl disulfide, aryl methyl sulfides, copper catalysis

Aryl methyl sulfide fragments commonly occur as key units in a variety of pharmaceuticals and biologically active molecules potentially useful in the treatment of such diseases as diabetes, inflammatory disease, Alzheimer's disease, or Parkinsonism.[1] In addition, these compounds can act as effective electrophiles for some transition-metal-catalyzed C–C,[2] C–N,[3] or C–B coupling reactions,[4] or can serve as reactants for carbothiolation of terminal alkynes.[5] Although considerable progress has been made in the conventional construction of C(aryl)–S bonds by cross-coupling of thiols with aryl halides or pseudohalides with various transition metals such as palladium,[6] nickel,[7] copper,[8] cobalt,[9] or indium[10] as catalysts, the synthesis of aryl methyl analogues in this fashion is challenging, presumably because of the instability and high volatility of methanethiol. Reliable approaches for the synthesis of aryl methyl sulfides include the reduction of the corresponding sulfoxides;[11] treatment of aryl thiols with iodomethane,[12] dimethyl carbonate,[13] or other sulfur-containing reagents such as sodium methanethiolate,[14] sulfur powder,[15] or *S*-methylisothiourea sulfate;[16] and the combination of masked inorganic sulfur and dimethyl carbonate with aryl halides.[17] In addition, dimethyl sulfoxide has recently emerged as an effective methylthiolation surrogate for coupling with aryl halides,[18] arylcarboxylic acids,[19] arenes, or heteroarenes.[20] Although various sulfur-transferring reagents can be used in the preparation of aryl methyl sulfides, dimethyl disulfide, a commercial food additive and sulfidation agent, continues to attract attention due to its high reactivity and relative stability compared with gaseous methanethiol. Accordingly, Taniguchi reported alkyl- or arylthiolations of aryl iodides with dimethyl disulfide and other disulfide compounds in the presence of a nickel catalyst and zinc under neutral conditions.[21] Morales-Morales and co-workers developed a similar procedure for aryl iodides or bromides catalyzed by a fluorinated bisimino nickel NNN pincer complex along with zinc.[22] Atom-economic directed *ortho*-lithiations of aryl C–H bonds have been developed by Stanetty et al.,[23] who used 1,1-dimethylethyl phenylcarbamate, and by Fort and Rodriquez, who used 2-chloropyridyl group complexation followed by electrophilic substitution with dimethyl disulfide. The use of dialkyl hydrazides for directed *ortho*-metalations was reported by Wuts and co-workers.[25] Subsequently, Yu and co-workers reported a $Cu(OAc)_2$-mediated methylthiolation of the C–H bond of 2-phenylpyridine with dimethyl disulfide under an air atmosphere.[26] Another direct thiolation of aryl C–H bonds with disulfides under palladium and copper co-catalysis was reported by Nishihara's group.[27]

Several other elegant protocols that apparently meet the requirements of green and sustainable chemistry have also been recently developed. For example, Wangelin and co-workers developed a mild metal-free synthesis of aryl methyl sulfides from arenediazonium salts and dimethyl disulfide in the presence of the organic dye eosin Y and visible-light irradiation or a weak and environmentally benign base.[28] At about the same time, we reported a transition-metal-free C–S bond formation from arylboronic acids and dimethyl disulfide under neutral conditions.[29] Moreover, a unified method for the thiolation of aryl or vinyl iodides with dimethyl disulfide by using the visible-light photocatalyst *fac*-Ir(ppy)$_3$ has been reported by Polyzos's group.[30]

Nevertheless, each of the procedures discussed above entails various disadvantages, such as the need to use expensive metals, stoichiometric amounts of transition-metal sources, appropriate ligands, prefunctionalized substrates, organic peroxides, environmentally damaging organic solvents, or harsh reaction conditions. Undoubtedly, an efficient and environmentally benign synthetic procedure would still be much appreciated. Considering that aryl iodides and bromides are readily accessible, inexpensive, and compatible with numerous functional groups, and that water is an ideal and ecofriendly solvent due to its lack of toxicity and wide availability, we wish to report a route to aryl methyl sulfides through the copper-catalyzed coupling of aryl iodides or bromides with dimethyl disulfide in neat water as a reaction medium.

Table 1 Screening of Reaction Conditions for C–S Coupling of *p*-Iodoanisole and Dimethyl Disulfide[a]



Entry	Catalyst	Base	Additive	Yield[b] (%)
1	Cu(acac)$_2$	Na_2CO_3	–	<5
2	Cu(acac)$_2$	Na_2CO_3	TBAB	40
3	Cu(OAc)$_2$·H_2O	Na_2CO_3	TBAB	48
4	$CuSO_4$·5H_2O	Na_2CO_3	TBAB	35
5	$CuCl_2$·2H_2O	Na_2CO_3	TBAB	38
6	$CuBr_2$	Na_2CO_3	TBAB	36
7	CuI	Na_2CO_3	TBAB	35
8	CuBr	Na_2CO_3	TBAB	28
9	CuCl	Na_2CO_3	TBAB	25
10	–	Na_2CO_3	TBAB	–
11	Cu(OAc)$_2$·H_2O	K_2CO_3	TBAB	50
12	Cu(OAc)$_2$·H_2O	Cs_2CO_3	TBAB	55
13	Cu(OAc)$_2$·H_2O	K_3PO_4·H_2O	TBAB	35
14	Cu(OAc)$_2$·H_2O	KF	TBAB	25
15	Cu(OAc)$_2$·H_2O	KOH	TBAB	78
16	Cu(OAc)$_2$·H_2O	NaOH	TBAB	75
17	Cu(OAc)$_2$·H_2O	–	TBAB	–
18	Cu(OAc)$_2$·H_2O	KOH	TBAF	74
19	Cu(OAc)$_2$·H_2O	KOH	TBAC	75
20	Cu(OAc)$_2$·H_2O	KOH	PEG-400	<5
21	Cu(OAc)$_2$·H_2O[c]	KOH	TBAB	70
22	Cu(OAc)$_2$·H_2O[d]	KOH	TBAB	78
23	Cu(OAc)$_2$·H_2O[e]	KOH	TBAB	77
24[f]	Cu(OAc)$_2$·H_2O	KOH	TBAB	72
25[g]	Cu(OAc)$_2$·H_2O	KOH	TBAB	77
26[h]	Cu(OAc)$_2$·H_2O	KOH	TBAB	78
27[i]	Cu(OAc)$_2$·H_2O	KOH	TBAB	65
28[j]	Cu(OAc)$_2$·H_2O	KOH	TBAB	79
29[k]	Cu(OAc)$_2$·H_2O	KOH	TBAB	78

[a] Reaction conditions: *p*-iodoanisole (1.0 mmol), dimethyl disulfide (1.2 mmol), catalyst (0.1 mmol), base (2 mmol), additive (0.05 mmol), H_2O (2.0 mL), under air, 12h, 100 °C.
[b] Isolated yield.
[c] 5 mol%.
[d] 15 mol%.
[e] 20 mol%
[f] Dimethyl disulfide (1.0 mmol).
[g] Dimethyl disulfide (1.5 mmol).
[h] Dimethyl disulfide (2.0 mmol).
[i] 80 °C.
[j] 120 °C.
[k] Under N_2.

We began our investigations by coupling of *p*-iodoanisole with dimethyl disulfide in the presence of Cu(acac)$_2$ as a catalyst and Na_2CO_3 as a base in a sealed tube with neat water as solvent under air. Although only a trace of the desired product was detected under these conditions (Table 1, entry 1), 4-(methoxy)thioanisole was obtained in 40% yield when 5 mol% of tetrabutylammonium bromide (TBAB) was added as a phase-transfer reagent at 100 °C for 12 hours (entry 2). Encouraged by this result, we attempted to optimize the reaction conditions further. First, we screened several Cu(II) salts [Cu(OAc)$_2$·H_2O, $CuSO_4$·5H_2O, $CuCl_2$·2H_2O, and $CuBr_2$] and various Cu(I) compounds (CuI, CuBr and CuCl) as catalysts for this transformation (entries 3–9). Cu(OAc)$_2$·H_2O as catalyst provided a markedly higher yield than any of the other copper sources. Under otherwise identical conditions, none of the target product was detected in the absence of a copper catalyst (entry 10). Subsequently, several bases were tested (entries 11–16), and the results suggested that KOH is the most suitable base for this transformation, furnishing in the product in 78% yield (entry 15). The reaction was sluggish in the absence of any base (entry 17). On replacement of TBAB with tetrabutylammonium fluoride (TBAF) or tetrabutylammonium chloride (TBAC), the methylthiolation product was obtained in comparable yields (entries 18 and 19), whereas only a small amount of desired product was detected when poly(ethylene glycol) (PEG-400) was used as the phase-transfer agent (entry 20). The effect of the amount of Cu(OAc)$_2$·H_2O was then examined, and it was found that the yield fell slightly on decreasing the amount of this catalyst but remained almost the same when 10 or 15mol% of the catalyst was used (entries 21–23). In addition, we found that the optimal amount of dimethyl disulfide relative to *p*-iodoanisole was 1.2 equivalents (entries 24–26). The yield dropped noticeably at a lower temperature (entry 27), while a comparable yield was obtained at a higher temperature (entry 28), so the optimal temperature for the current reaction is 100 °C. Moreover, changing the atmosphere from air to nitrogen did not increase the conversion (entry 29), making the reaction manipulatively simple and convenient. On the basis of these results, it appeared that the optimal conditions for the cross-coupling of *p*-iodoanisole with dimethyl disulfide in water involve the use of $Cu(OAc)_2{\cdot}H_2O$ as catalyst, KOH as base, and TBAB as phase-transfer reagent at 100 °C for 12 hours under air.

To further explore the generality and scope of this protocol, a wide array of aryl iodides were examined. Specifically, iodobenzene and aryl iodides with electron-donating substituents, including OMe, SMe, Me, or NH_2 groups, were compatible with this procedure and afforded the corresponding methylthiolation products in satisfactory yields (Table 2, entries 1–10). Notably, the preserved amino group is attractive because most arylamines can be easily transformed into various arenediazonium salts that have superior reactivity to the corresponding aryl halides and can consequently serve as useful partners in palladium-catalyzed carbon–carbon or carbon–heteroatom cross-coupling reactions.[31] Moreover, the reaction was highly chemoselective towards other halogen groups of aryl iodides. In other words, the respective desired products were obtained in good yields while fluoro, chloro, or bromo groups remained intact, which might facilitate further functionalization of the phenyl ring (entries 11–20). In the case of 1,4-diiodobenzene, the monomethylthiolation product was obtained together with the bismethylthiolation product, even though an excess of dimethyl disulfide was used. Aryl iodides with electron-withdrawing substituents such as NO_2 and CN groups were also good coupling partners (entries 21–24). It is noteworthy that, like *para*- or *meta*-substituted aryl iodides, the corresponding *ortho*-substituted substrates also reacted smoothly with dimethyl disulfide, albeit giving the desired products in moderate yields. The hetaryl analogues 2- and 3-iodopyridine reacted readily to provide the corresponding hetaryl methyl sulfides which are of much interest for their biological activities (entries 25 and 26).

Further experiments showed that bromobenzene and *p*-tolyl bromide were not very reactive under our reaction conditions, whereas aryl bromides with electron-withdrawing substituents such as NO_2 or CN showed better reactivity for this transformation (Table 3, entries 1–5). To our delight, the hetaryl analogues 2-bromopyridine, 3-bromopyridine, 3-bromoquinoline, and 4-bromoisoquinoline reacted readily to afford the desired products in acceptable yields (entries 6–9). Furthermore, although the yield from *p*-iodoanisole did not change markedly on increasing the temperature above 100 °C, elevating the reaction temperature to 130 °C significantly improved the yields from aryl bromides. As expected, only a trace of amount of product was detected when 1-chloro-4-nitrobenzene was used as substrate under the standard conditions (entry 10).

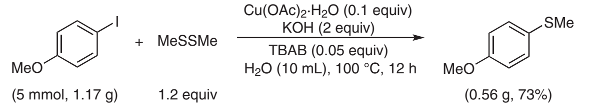
To further demonstrate the synthetic utility of this strategy, a representative gram-scale reaction of *p*-iodoanisole with dimethyl disulfide was explored, and the expected product was obtained in a satisfactory 73% yield (Scheme 1).

Table 2 Methylthiolation of Aryl Iodides with Dimethyl Disulfide[a,32]

$$\text{ArI} + \text{MeSSMe} \xrightarrow[\text{TBAB, H}_2\text{O, 100 °C}]{\text{Cu(OAc)}_2\cdot\text{H}_2\text{O, KOH}} \text{ArSMe}$$

Entry	Ar	Yield[b] (%)
1	Ph	76
2	4-$MeOC_6H_4$	78
3	3-$MeOC_6H_4$	75
4	2-$MeOC_6H_4$	58
5	3-$MeSC_6H_4$	70
6	4-MeC_6H_4	72
7	3-MeC_6H_4	68
8	2,4,6-$Me_3C_6H_2$	45
9	4-$H_2NC_6H_4$	77
10	2-$H_2NC_6H_4$	70
11	4-IC_6H_4	50
12	4-BrC_6H_4	71
13	3-BrC_6H_4	60
14	4-ClC_6H_4	78
15	3-ClC_6H_4	67
16	2-ClC_6H_4	48
17	3,5-$Cl_2C_6H_3$	50
18	4-FC_6H_4	65
19	3-FC_6H_4	58
20	2-FC_6H_4	52
21	4-$O_2NC_6H_4$	80
22	3-$O_2NC_6H_4$	78
23	4-NCC_6H_4	74
24	3-NCC_6H_4	70
25	2-pyridyl	65
26	3-pyridyl	60

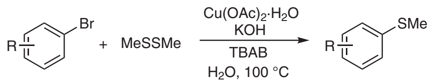
[a] Reaction conditions: ArI (1.0 mmol), dimethyl disulfide (1.2 mmol), $Cu(OAc)_2{\cdot}H_2O$ (0.1 mmol), KOH (2.0 mmol), TBAB (0.05 mmol), H_2O (2.0 mL), 100 °C, 12 h.
[b] Isolated yield.



Scheme 1 Gram-scale reaction

To investigate the reaction mechanism, we performed a radical-trap experiment. In the presence of an excess of the radical scavenger 2,2,6,6-tetramethylpiperidine *N*-oxide (TEMPO) or butylated hydroxytoluene (BHT), coupling of *p*-iodoanisole with dimethyl disulfide under otherwise iden-

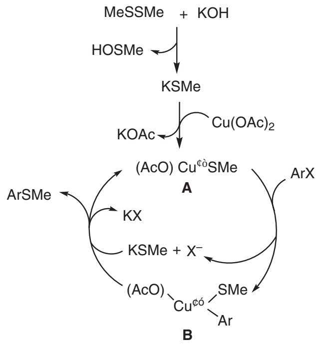
Table 3 Methylthiolation of Aryl Bromides with Dimethyl Disulfide[a,32]



Entry	Ar	Yield[b] (%)
1	H	15 (38)
2	4-MeC_6H_4	12 (35)
3	4-$O_2NC_6H_4$	55 (70)
4	2-$O_2NC_6H_4$	48 (65)
5	4-NCC_6H_4	45 (66)
6	2-pyridyl	38 (60)
7	3-pyridyl	32 (52)
8	quinolin-3-yl	30 (48)
9	isoquinoline-4-yl	35 (52)
10[c]	2-$O_2NC_6H_4$	(8)

[a] Reaction conditions: aryl halide (1.0 mmol), dimethyl disulfide (1.2 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), KOH (2.0 mmol), TBAB (0.05 mmol), H_2O (2.0 mL), 100 °C, 12 h.
[b] Isolated yield. Yields obtained at 130 °C are shown in parentheses.
[c] 2-$O_2NC_6H_4Cl$.

tical conditions still took place. These results suggested that the current methylthiolation does not involve radicals. On the basis of the above results and reports in the literature,[20b,d,g,33] a plausible reaction pathway for the reaction was proposed (Scheme 2). Initially, in the presence of base, KSMe is generated from dimethyl disulfide, along with HOSMe. The reactive sulfhydryl ion intermediate MeS^- then reacts with $Cu(OAc)_2$ to form species **A**, which adds to the aryl halide and oxidatively produces intermediate **B** together with a halide ion X^-. Reaction of **B** with KSMe provides the desired product together with KX, completing the catalytic cycle.



Scheme 2 Plausible mechanism for the methylthiolation

In conclusion, a practical protocol for methylthiolation of aryl iodides or bromides with dimethyl disulfide has been developed that uses neat water as the reaction medium. This procedure dispenses with a ligand, an inert atmosphere, and a dry nonaqueous solvent, and is tolerant of structurally diverse substrates, making it a powerful complement to common approaches to the synthesis of a broad range of aryl methyl sulfides.

Funding Information

We are grateful for financial support from the Natural Science Foundation of Zhejiang Province (No. LY18B020004) and the National Natural Science Foundation of China (No. 21572094).

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707131.

References and Notes

(1) (a) Kalgutkar, A. S.; Kozak, K. R.; Crews, B. C.; Marnett, L. J. *J. Med. Chem.* **1998**, *41*, 4800. (b) Laufer, S. A.; Striegel, H.-G.; Wagner, G. K. *J. Med. Chem.* **2002**, *45*, 4695. (c) Laufer, S. A.; Zimmermann, W.; Ruff, K. J. *J. Med. Chem.* **2004**, *47*, 6311. (d) Gallardo-Godoy, A.; Fierro, A.; McLean, T. H.; Castillo, M.; Cassels, B. K.; Reyes-Parada, M.; Nichols, D. E. *J. Med. Chem.* **2005**, *48*, 2407. (e) Pradhan, T. K.; De, A.; Mortier, J. *Tetrahedron* **2005**, *61*, 9007.

(2) (a) Dubbaka, S. R.; Vogel, P. *Angew. Chem. Int. Ed.* **2005**, *44*, 7674. (b) Peña-Cabrera, E.; Aguilar-Aguilar, A.; González-Domínguez, M.; Lager, E.; Zamudio-Vázquez, R.; Godoy-Vargas, J.; Villanueva-García, F. *Org. Lett.* **2007**, *9*, 3985. (c) Prokopcová, H.; Kappe, C. O. *Angew. Chem. Int. Ed.* **2009**, *48*, 2276. (d) Metzger, A.; Melzig, L.; Despotopoulou, C.; Knochel, P. *Org. Lett.* **2009**, *11*, 4228. (e) Melzig, L.; Metzger, A.; Knochel, P. *J. Org. Chem.* **2010**, *75*, 2131. (f) Melzig, L.; Metzger, A.; Knochel, P. *Chem. Eur. J.* **2011**, *17*, 2948. (g) Ookubo, Y.; Wakamiya, A.; Yorimitsu, H.; Osuka, A. *Chem. Eur. J.* **2012**, *18*, 12690. (h) Modha, S. G.; Mehta, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2013**, *42*, 5042. (i) Hooper, J. F.; Young, R. D.; Pernik, I.; Weller, A. S.; Willis, M. C. *Chem. Sci.* **2013**, *4*, 1568. (j) Liu, J.; Liu, Y.; Du, W.; Dong, Y.; Liu, J.; Wang, M. *J. Org. Chem.* **2013**, *78*, 7293. (k) Pan, F.; Wang, H.; Shen, P.-X.; Zhao, J.; Shi, Z.-J. *Chem. Sci.* **2013**, *4*, 1573. (l) Wang, L.; He, W.; Yu, Z. *Chem. Soc. Rev.* **2013**, *42*, 599. (m) Pan, F.; Shi, Z.-J. *ACS Catal.* **2014**, *4*, 280. (n) Otsuka, S.; Fujino, D.; Murakami, K.; Yorimitsu, H.; Osuka, A. *Chem. Eur. J.* **2014**, *20*, 13146. (o) Quan, Z.-J.; Lv, Y.; Jing, F.-Q.; Jia, X.-D.; Huo, C.-D.; Wang, X.-C. *Adv. Synth. Catal.* **2014**, *356*, 325. (p) Zhu, F.; Wang, Z.-X. *Org. Lett.* **2015**, *17*, 1601.

(3) (a) Ram, V. J.; Agarwal, N. *Tetrahedron Lett.* **2001**, *42*, 7127. (b) Sugahara, T.; Murakami, K.; Yorimitsu, H.; Osuka, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 9329. (c) Wang, X.; Tang, Y.; Long, C.-Y.; Dong, W.-K.; Li, C.; Xu, X.; Zhao, W.; Wang, X.-Q. *Org. Lett.* **2018**, *20*, 4749.

(4) (a) Uetake, Y.; Niwa, T.; Hosoya, T. *Org. Lett.* **2016**, *18*, 2758. (b) Bhanuchandra, M.; Baralle, A.; Otsuka, S.; Nogi, K.; Yorimitsu, H.; Osuka, A. *Org. Lett.* **2016**, *18*, 2966.

(5) (a) Hooper, J. F.; Chaplin, A. B.; González-Rodríguez, C.; Thompson, A. L.; Weller, A. S.; Willis, M. C. *J. Am. Chem. Soc.* **2012**, *134*, 2906. (b) Arambasic, M.; Hooper, J. F.; Willis, M. C.

Org. Lett. **2013**, *15*, 5162. (c) Iwasaki, M.; Topolovčan, N.; Hu, H.; Nishimura, Y.; Gagnot, G.; Nanakorn, R.; Yuvacharaskul, R.; Nakajima, K.; Nishihara, Y. *Org. Lett.* **2016**, *18*, 1642.

(6) (a) Migita, T.; Shimizu, T.; Asami, Y.; Shiobara, J.-i.; Kato, Y.; Kosugi, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1385. (b) Mann, G.; Baranano, D.; Hartwig, J. F.; Rheingold, A. L.; Guzei, I. A. *J. Am. Chem. Soc.* **1998**, *120*, 9205. (c) Li, G. Y.; Zheng, G.; Noonan, A. F. *J. Org. Chem.* **2001**, *66*, 8677. (d) Itoh, T.; Mase, T. *Org. Lett.* **2004**, *6*, 4587. (e) Mispelaere-Canivet, C.; Spindler, J.-F.; Perrio, S.; Beslin, P. *Tetrahedron* **2005**, *61*, 5253. (f) Fernández-Rodríguez, M. A.; Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 2180. (g) Dahl, T.; Tornøe, C. W.; Bang-Andersen, B.; Nielsen, P.; Jørgensen, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 1726. (h) Lee, C.-F.; Liu, Y.-C.; Badsara, S. S. *Chem. Asian J.* **2014**, *9*, 706.

(7) (a) Cristau, H. J.; Chabaud, B.; Chêne, A.; Christol, H. *Synthesis* **1981**, *1981*, 892. (b) Percec, V.; Bae, J.-Y.; Hill, D. H. *J. Org. Chem.* **1995**, *60*, 6895. (c) Millois, C.; Diaz, P. *Org. Lett.* **2000**, *2*, 1705. (d) Zhang, Y.; Ngeow, K. C.; Ying, J. Y. *Org. Lett.* **2007**, *9*, 3495.

(8) (a) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 3517. (b) Bates, C. G.; Gujadhur, R. K.; Venkataraman, D. *Org. Lett.* **2002**, *4*, 2803. (c) Enguehard-Gueiffier, C.; Thery, I.; Gueiffier, A.; Buchwald, S. L. *Tetrahedron* **2006**, *62*, 6042. (d) Carril, M.; SanMartin, R.; Dominguez, E.; Tellitu, I. *Chem. Eur. J.* **2007**, *13*, 5100. (e) Zhang, H.; Cao, W.; Ma, D. *Synth. Commun.* **2007**, *37*, 25. (f) Chen, Y.-J.; Chen, H.-H. *Org. Lett.* **2006**, *8*, 5609. (g) Verma, A. K.; Singh, J.; Chaudhary, R. *Tetrahedron Lett.* **2007**, *48*, 7199. (h) Lv, X.; Bao, W. *J. Org. Chem.* **2007**, *72*, 3863.

(9) Wong, Y.-C.; Jayanth, T. T.; Cheng, C.-H. *Org. Lett.* **2006**, *8*, 5613.

(10) (a) Reddy, V. P.; Swapna, K.; Kumar, A. V.; Rao, K. R. *J. Org. Chem.* **2009**, *74*, 3189. (b) Reddy, V. P.; Swapna, K.; Kumar, A. V.; Swapna, K.; Rao, K. R. *Org. Lett.* **2009**, *11*, 1697.

(11) (a) Kukushkin, V. Y. *Coord. Chem. Rev.* **1995**, *139*, 375. (b) Fernandes, A. C.; Fernandes, J. A.; Romão, C. C.; Veiros, L. F.; Calhorda, M. J. *Organometallics* **2010**, *29*, 5517. (c) Cardoso, J. M. S.; Royo, B. *Chem. Commun.* **2012**, *48*, 4944.

(12) Basu, B.; Paul, S.; Nanda, A. K. *Green Chem.* **2010**, *12*, 767.

(13) Glasnov, T. N.; Holbrey, J. D.; Kappe, C. O.; Seddon, K. R.; Yan, T. *Green Chem.* **2012**, *14*, 3071.

(14) Testaferri, L.; Tiecco, M.; Tingoli, M.; Bartoli, D.; Massoli, A. *Tetrahedron* **1985**, *41*, 1373.

(15) Jiang, Y.; Qin, Y.; Xie, S.; Zhang, X.; Dong, J.; Ma, D. *Org. Lett.* **2009**, *11*, 5250.

(16) Zhang, C.; Zhou, Y.; Huang, J.; Tu, C.; Zhou, X.; Yin, G. *Org. Biomol. Chem.* **2018**, *16*, 6316.

(17) Wang, M.; Qiao, Z.; Zhao, J.; Jiang, X. *Org. Lett.* **2018**, *20*, 6193.

(18) (a) Luo, F.; Pan, C.; Li, L.; Chen, F.; Cheng, J. *Chem. Commun.* **2011**, *47*, 5304. (b) Joseph, P. J. A.; Priyadarshini, S.; Kantam, M. L.; Sreedhar, B. *Tetrahedron* **2013**, *69*, 8276. (c) Ghosh, K.; Ranjit, S.; Mal, D. *Tetrahedron Lett.* **2015**, *56*, 5199.

(19) (a) She, J.; Jiang, Z.; Wang, Y. *Tetrahedron Lett.* **2009**, *50*, 593. (b) Fu, Z.; Li, Z.; Xiong, Q.; Cai, H. *Eur. J. Org. Chem.* **2014**, *2014*, 7798.

(20) (a) Chu, L.; Yue, X.; Qing, F.-L. *Org. Lett.* **2010**, *12*, 1644. (b) Dai, C.; Xu, Z.; Huang, F.; Yu, Z.; Gao, Y.-F. *J. Org. Chem.* **2012**, *77*, 4414. (c) Patil, S. M.; Kulkarni, S.; Mascarenhas, M.; Sharma, R.; Roopan, S. M.; Roychowdhury, A. *Tetrahedron* **2013**, *69*, 8255. (d) Sharma, P.; Rohilla, S.; Jain, N. *J. Org. Chem.* **2015**, *80*, 4116. (e) Zou, J.-F.; Huang, W.-S.; Li, L.; Xu, Z.; Zheng, Z.-J.; Yang, K.-F.; Xu, L.-W. *RSC Adv.* **2015**, *5*, 30389. (f) Xu, Y.; Cong, T.; Liu, P.; Sun, P. *Org. Biomol. Chem.* **2015**, *13*, 9742. (g) Ravi, C.; Mohan, D. C.; Adimurthy, S. *Org. Biomol. Chem.* **2016**, *14*, 2282.

(21) Taniguchi, N. *J. Org. Chem.* **2004**, *69*, 6904.

(22) Baldovino-Pantaleón, O.; Hernández-Ortega, S.; Morales-Morales, D. *Adv. Synth. Catal.* **2006**, *348*, 236.

(23) Stanetty, P.; Koller, H.; Mihovilovic, M. *J. Org. Chem.* **1992**, *57*, 6833.

(24) Fort, Y.; Rodriguez, A. L. *J. Org. Chem.* **2003**, *68*, 4918.

(25) Pratt, S. A.; Goble, M. P.; Mulvaney, M. J.; Wuts, P. G. M. *Tetrahedron Lett.* **2000**, *41*, 3559.

(26) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. *J. Am. Chem. Soc.* **2006**, *128*, 6790.

(27) Iwasaki, M.; Iyanaga, M.; Tsuchiya, Y.; Nishimura, Y.; Li, W.; Li, Z.; Nishihara, Y. *Chem. Eur. J.* **2014**, *20*, 2459.

(28) (a) Majek, M.; Wangelin, A. J. V. *Chem. Commun.* **2013**, *49*, 5507. (b) Koziakov, D.; Majek, M.; von Wangelin, A. J. *Org. Biomol. Chem.* **2016**, *14*, 11347.

(29) Wu, X.-m.; Lou, J.-m.; Yan, G.-b. *Synlett* **2016**, *27*, 2269.

(30) Czyz, M. L.; Weragoda, G. K.; Monaghan, R.; Connell, T. U.; Brzozowski, M.; Scully, A. D.; Burton, J.; Lupton, D. W.; Polyzos, A. *Org. Biomol. Chem.* **2018**, *16*, 1543.

(31) Roglans, A.; Pla-Quintana, A.; Moreno-Mañas, M. *Chem. Rev.* **2006**, *106*, 4622.

(32) **(Het)aryl Methyl Sulfides; General Procedure**

A 25-mL sealable tube was charged with the appropriate aryl iodide or bromide (1.0 mmol), dimethyl disulfide (1.2 mmol), $Cu(OAc)_2\cdot H_2O$ (0.1 mmol), KOH (2.0 mmol), TBAB (0.05 mmol), and H_2O (2.0 mL). The mixture was stirred at 100 °C (130 °C for bromides) for 12 h under air then cooled to r.t. The mixture was diluted with H_2O (5 mL) and extracted with EtOAc (4 × 10 mL). The extracts were combined, washed with brine (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography [silica gel, EtOAc–hexane (1:30 to 1:100)].

4-(Methylsulfanyl)aniline (Table 2, entry 9)

Yellow oil; yield: 107 mg (77%). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.16$ (d, $J = 8.7$ Hz, 2 H), 6.60 (d, $J = 8.4$ Hz, 2 H), 3.62 (s, 2 H), 2.39 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 145.2$, 131.1, 125.7, 115.9, 18.8. GC/MS (EI): $m/z = 139$ [M+].

1-Methoxy-4-(methylsulfanyl)benzene; Gram-Scale Synthesis

A 50 mL sealable tube was charged with *p*-iodoanisole (5 mmol, 1.17 g), dimethyl disulfide (6 mmol, 0.56 g), $Cu(OAc)_2\cdot H_2O$ (0.5 mmol, 100 mg), KOH (10 mmol, 5.6 g), TBAB (0.25 mmol, 81 mg), and H_2O (10 mL). The mixture was stirred at 100 °C for 12 h under air, then cooled to r.t., diluted with H_2O (5 mL), and extracted with EtOAc (4 × 15 mL). The extracts were combined and washed with brine (3 × 15 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was purified by chromatography [silica gel, EtOAc–hexane (1:30)] to give a pale-yellow oil; yield: 0.56 g (73%).

(33) (a) Xu, H.-J.; Zhao, Y.-Q.; Feng, T.; Feng, Y.-S. *J. Org. Chem.* **2012**, *77*, 2878. (b) Wang, F.; Chen, C.; Deng, G.; Xi, C. *J. Org. Chem.* **2012**, *77*, 4148. (c) He, G.; Huang, Y.; Tong, Y.; Zhang, J.; Zhao, D.; Zhou, S.; Han, S. *Tetrahedron Lett.* **2013**, *54*, 5318. (d) Taniguchi, N. *Eur. J. Org. Chem.* **2014**, *2014*, 5691. (e) Rostami, A.; Rostami, A.; Ghaderi, A. *J. Org. Chem.* **2015**, *80*, 8694. (f) Liu, Z.; Ouyang, K.; Yang, N. *Org. Biomol. Chem.* **2018**, *16*, 988. (g) Deng, K.-Z.; Zhang, L.-L.; Chen, Y.-F.; Xie, H.-X.; Xu, X.-B.; Xia, C.-C.; Ji, Y.-F. *Org. Biomol. Chem.* **2019**, *17*, 7055.