doi:10.1246/cl.2011.1254

$FeCl_3$-mediated Direct Chalcogenation of Phenols

Kimihiro Komeyama,* Kiyoto Aihara, Tetsuya Kashihara, and Ken Takaki*
Department of Applied Chemistry, Graduate School of Engineering, Hiroshima University,
Higashi-Hiroshima, Hiroshima 739-8527

(Received August 18, 2011; CL-110694; E-mail: kkome@hiroshima-u.ac.jp)

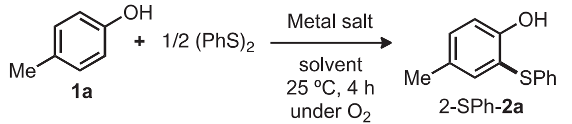
Direct sulfenylation and selenylation of phenols using a stoichiometric amount of $FeCl_3$ under an oxygen atmosphere has been developed. The chalcogenated phenols were shown to be suitable for preparing *S*- and *Se*-containing compounds using the reaction of the remaining hydroxy group.

Aromatic thio- and seleno-ethers are valuable motifs. In particular, diaryl sulfides and selenides are frequently found in biological and pharmaceutical active molecules[1] and drugs.[2] To synthesize these molecules, numerous procedures have been explored; for example, classical methods using thermal[3] and basic[4] reactions reported. Recently, these have been improved by using more powerful methods involving transition-metal catalysts.[5] However, direct chalcogenation of aromatic C–H bonds is limited to highly nucleophilic aromatics like indoles,[6] that of other aromatic compounds are rare.[7]

Phenols are key intermediates and show attractive reactivities in organic synthesis. For instance, they can be transformed to diaryl ethers by means of Ullmann-type cross-coupling reactions.[8] Moreover, they can be easily converted to the pseudohalide-like sulfonates and sulfonamides which enable various cross-coupling reactions.[9] Despite their unique reactivity and widespread utilization, few practical methods for sulfenylation and selenylation of phenols have been reported.[7a–7e] These methods require a large excess of dichalcogenides (or phenols) and harsh reaction conditions, resulting in low product yields and narrow substrate scope. During our study of new synthetic utilizations with iron complexes, it was discovered that an iron salt like $FeCl_3$ was a highly effective reagent for the sulfenylation and selenylation of phenols, making the synthesis of a wide range of chalcogenated phenols possible under an oxygen atmosphere.

When 4-cresol (**1a**) was treated with diphenyl disulfide and $FeCl_3$ (1.0 equiv) in DCM at 25 °C for 4 h under O_2, 2-phenylsulfanyl-4-cresol (2-SPh-**2a**) was obtained in 96% yield (Entry 1, Table 1). The presence of molecular oxygen and a stoichiometric amount of $FeCl_3$ were crucial for the reaction to proceed efficiently. Thus, if the reaction was carried out under argon or by using 10 or 50 mol % of $FeCl_3$ this resulted in a low yield (Entries 8 and 9). More loading of $FeCl_3$ (2 equiv) increased the consumption rate of both the substrates (1.5 h), although an oxidative homocoupling product, 2,2′-biphenol, and other unasignable products were obtained. In addition, the reaction under argon or air atmosphere gave lower yield (Entries 10 and 11). For this direct sulfenylation, nonpolar solvents such as DCM, $MeNO_2$, DCE, and toluene were suitable (Entries 2–4). In contrast, Et_2O, MeCN, and THF gave sluggish yields of 2-SPh-**2a** (Entries 5–7). Sulfenylation using $FeBr_3$ also provided the desired product in a moderate yield (Entry 12), but it occurred alongside the bromination of **1a**. Other iron and transition-metal complexes like $[Fe(acac)_3]$, $FeCl_2$, $CuCl_2$, $Cu(OAc)_2$, $[CuCl(OH)(tmeda)]$, and $ZnCl_2$ were not effective at all in the reaction (Entries 13–18). It is known that $BF_3{\cdot}OEt_2$ and $AlCl_3$ are effective reagents for the activation of disulfides to provide *S*-substituted sulfonium ions $\{RS^+(LA^-)\text{-}SR\}$, which has good electrophilic character.[10] However, these Lewis acids did not work well in the sulfenylation (Entries 19 and 20).

Table 1. Screening of reaction conditions for the reaction of 4-cresol and diphenyl disulfide[a]

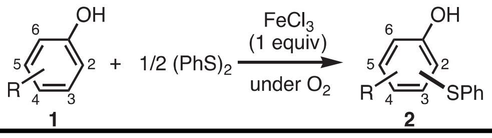


Entry	Metal (equiv)	Solvent	Yield of 2-SPh-**2a**[b]/%
1	$FeCl_3$ (1)	DCM	96 (88)
2	$FeCl_3$ (1)	$MeNO_2$	82
3	$FeCl_3$ (1)	DCE	59
4	$FeCl_3$ (1)	Toluene	40
5	$FeCl_3$ (1)	Et_2O	8
6	$FeCl_3$ (1)	MeCN	3
7	$FeCl_3$ (1)	THF	2
8	$FeCl_3$ (0.5)	DCM	35
9	$FeCl_3$ (0.1)	DCM	5
10[c]	$FeCl_3$ (1)	DCM	35
11[d]	$FeCl_3$ (1)	DCM	40
12	$FeBr_3$ (1)	DCM	45
13	$Fe(acac)_3$ (1)	DCM	0
14	$FeCl_2$ (1)	DCM	0
15	$CuCl_2$ (1)	DCM	3
16	$Cu(OAc)_2$ (1)	DCM	0
17	CuCl(OH)(TMEDA) (1)	DCM	0
18	$ZnCl_2$ (1)	DCM	0
19	$BF_3{\cdot}OEt_2$ (1)	DCM	0
20	$AlCl_3$ (1)	DCM	3

[a]Reaction conditions: **1a** (1.0 mmol), $(PhS)_2$ (0.5 mmol), $FeCl_3$ (0.5 mmol), solvent (0.5 mL). [b]GC yield. Isolated yield is shown in parentheses. [c]The reaction was carried out under argon. [d]The reaction was carried out under air.

Once the optimal conditions had been established, the use of various phenols in the sulfenylation was then explored. These results are summarized in Table 2. 4-Substituted phenols were smoothly sulfenylated at the 2-position (Entries 1–7, Table 2). The reactions of the phenols possessing electron-withdrawing groups, CO_2Me (**1e**) and CHO (**1f**), required a high temperature (80 °C) to generate satisfactory yields of the product (Entries 4 and 5). Interestingly, in the case of **1f**, although the conversion of substrates was very low (each ca. 30%), the sulfenylated

Table 2. Reaction of various phenols with diphenyl disulfide[a]



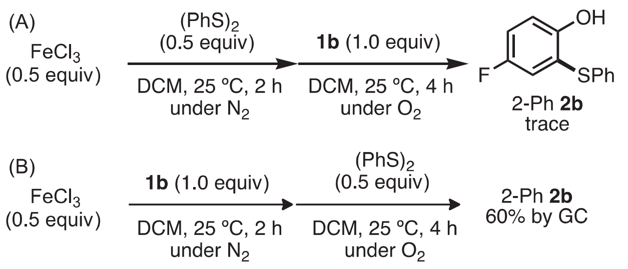
Entry	R (**1**)	Temp /°C	Time /h	Products **2** and yield/%[b]		
				2-SPh	3-SPh	4-SPh
1	4-F (**1b**)	25	4	70	0	—
2	4-Cl (**1c**)	25	5	61	0	—
3	4-Br (**1d**)	25	4	51	0	—
4[c]	4-CO_2Me (**1e**)	80	7	77	0	—
5[c]	4-CHO (**1f**)	80	8	17	0	—
6[c]	4-OH (**1g**)	50	4	50 (25)[d]	0	—
7[c]	4-OMe (**1h**)	50	6	44 (19)[d]	0	—
8	5-F (**1i**)	25	6	86	0	8
9	5-Br (**1j**)	25	6	52	0	38
10[c]	5-Me (**1k**)	80	6	63 (15)[e]	0	26
11[c]	5-OMe (**1l**)	80	6	78	0	0
12	5-*t*-Bu (**1m**)	25	7	95	0	0
13	6-F (**1n**)	25	7	23	0	34
14	6-I (**1o**)	25	5	21	20	47
15[c]	6-CO_2Me (**1p**)	80	4	0	0	78
15[c]	6-Me (**1q**)	80	6	32	0	67
16[f]	4-Me (**1a**)	25	5	88	0	—

[a]Reaction conditions: **1** (1.0 mmol), $(PhS)_2$ (0.5 mmol), $FeCl_3$ (0.5 mmol), DCM (0.5 mL). [b]Isolated yield. [c]$MeNO_2$ was used instead of DCM. [d]The yield of 2,5-disulfenylated products. [e]The yield of 6-sulfenylated product. [f]$(MeS)_2$ was used instead of $(PhS)_2$.

product 2-SPh-**2f** was afforded in 17% yield without the loss of the formyl group (Entry 5). Phenols having electron-donating groups such as OH (**1g**) and OMe (**1h**) were more reactive, giving rise to monosulfenylated products 2-SPh-**2g** (50%) and 2-SPh-**2h** (44%) with a formation of disulfenylated products at the 2- and 5-positions (Entries 6 and 7). In the reaction of 5-substituted phenols, the sulfenylation occurred selectively at the less hindered 2-position (Entries 8–12). In contrast, the reaction of 6-substituted phenols mainly occurred at the 4-position (Entries 13–15). Additionally, dialkyl disulfides like $(MeS)_2$ could also take part in this reaction to lead to alkyl aryl sulfides (Entry 16).

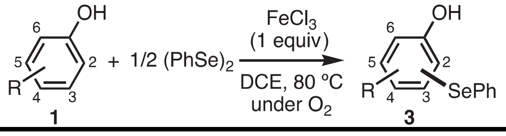
For the present reaction, the role of the iron salt has not been made clear, yet. Wang and Zeni suggested that $FeCl_3$ would be reduced with diaryl dichalcogenides like $(ArY)_2$ (Y = S or Se).[11] Based on these reports, we tested the possibility of this reduction in the present sulfenylation (Scheme 1). When $FeCl_3$ was reacted with $(PhS)_2$ under N_2 at 25 °C, an orange solution was obtained (Scheme 1A).[12] After that, the solution was treated with 4-fluorophenol (**1b**) under O_2, wherein a trace amount of the sulfenylated phenol 2-Ph-**2b** was detected. In sharp contrast, initial exposure of $FeCl_3$ with **1b** afforded a brown solution (Scheme 1B), which was sequentially reacted with $(PhS)_2$ under O_2 to provide 2-Ph-**2b** in 60% yield.[13]

These results might indicate the generation of the iron–phenoxide during the reaction. That is, it is known that $FeCl_3$ reacts with the phenol to give the iron–phenoxide,[14] which is shown as an intermediate in the iron-mediated and -catalyzed oxidative coupling of phenol derivatives.[15] Moreover, aryl- and alkyl-radicals could be captured with disulfides and diselenides.[16] Additionally, an addition of base such as 2,6-di-*tert*-butylpyridine or Et_3N (2 equivalents based on $FeCl_3$) did not prevent the sulfenylation.[21] In view of these facts, the present reaction might involve the trapping of the generated aryl radicals with the disulfide.



Scheme 1.

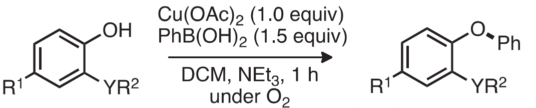
Table 3. Reaction of various phenols with diphenyl diselenide[a]



Entry	R (**1**)	Time/h	Products **3** and yield/%[b]		
			2-SePh	3-SePh	4-SePh
1	4-Me (**1a**)	25	54	0	—
2	4-Cl (**1c**)	25	93	0	—
3	4-Br (**1d**)	25	86	0	—
4	4-CO_2Me (**1e**)	24	69	0	—
5	5-F (**1i**)	24	25	0	62
6	5-Br (**1j**)	24	13	0	30
7	5-Me (**1k**)	24	33	0	33
8	5-OMe (**1l**)	24	48	4	10
9	5-*t*-Bu (**1m**)	24	73	0	0
10	6-F (**1n**)	24	14	0	82
11	6-Me (**1q**)	24	11	0	74

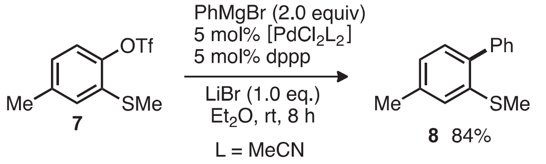
[a]Reaction conditions: **1** (1.0 mmol), $(PhSe)_2$ (0.5 mmol), $FeCl_3$ (0.5 mmol), DCE (1.0 mL). [b]Isolated yield.

Next, the $FeCl_3$-mediated system was applied to the selenylation of phenols using diphenyl diselenide (Table 3). This selenylation also required an O_2 atmosphere.[17] Similar to the above sulfenylation, various 4-, 5-, and 6-substituted phenols were converted to the corresponding monoselenylated compounds **3**. However, the regioselectivity was slightly different from the above described sulfenylation. In particular, the selenylation of 5-substituted phenols **1i**, **1j**, and **1k** selectively proceeded at the 4-position (Entries 5–7), while that of similar phenols, but with more electron-donating functions and bulkier ones, mainly occurred at the 2-position (Entries 8 and 9).

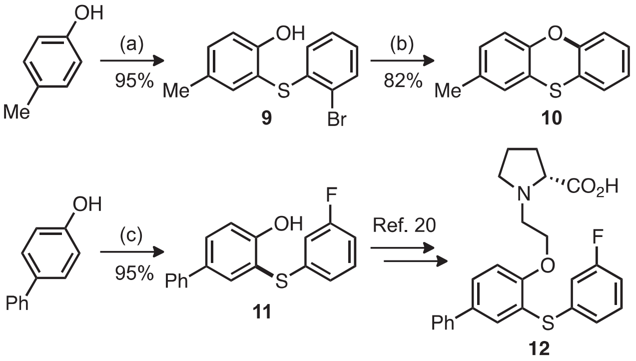


(1)

4 (R^1, YR^2 = Me, SMe), 54%
5 (R^1, YR^2 = Cl, SePh), 43%
6 (R^1, YR^2 = Br, SePh), 38%



(2)



Scheme 2. (a) $FeCl_3$ (0.5 equiv), $(2\text{-}BrC_6H_4S)_2$ (0.5 equiv), DCM, 25 °C, 6 h, O_2; (b) CuTC (1.0 equiv), DMAc, 100 °C, 2 h; (c) $FeCl_3$ (0.5 equiv), $(4\text{-}PhC_6H_4S)_2$ (0.5 equiv), $MeNO_2$, 80 °C, 6 h, O_2.

These chalcogenated phenols obtained in the present reactions could be used to synthesize S- and Se-containing compounds by means of the transformation of the remaining hydroxy group. Thus, the sulfenylated and selenylated phenols were reacted with arylboronic acids in the presence of copper(II) acetate to provide MeS- and PhSe-substituted diaryl ether (eq 1).[8] Moreover, the protected phenol **7** derived from 2-SMe-**2a** could react with the aryl-Grignard reagent in the presence of a palladium catalyst, giving rise to a biaryl structure possessing an SMe group (eq 2).[18] In addition, the present sulfenylation was capable of producing halogen-containing diaryl disulfides such as $(2\text{-}BrC_6H_4S)_2$ and $(3\text{-}FC_6H_4S)_2$, leading to the corresponding diaryl sulfide **9** and **11** in good yields under identical conditions (Scheme 2). The hydroxy function and aryl bromide moiety of the diaryl sulfide **9** reacted intramolecularly using copper(I)-thiophene-2-carboxylate (CuTC) to give the phenoxathiin skeleton **10**.[19] Diaryl sulfide **11** is a key intermediate in the synthesis of **12**, which serves as a Gly-T1 inhibitor.[20]

In conclusion, the $FeCl_3$-mediated direct synthesis of sulfenylated or selenylated phenols was shown using the chalcogenation of various phenols with diaryl disulfides or diaryl diselenides with chemo- and regioselectivity. In these reactions, the presence of an oxidant like molecular oxygen and a stoichiometric amount of $FeCl_3$ were crucial for these reactions to proceed efficiently. In addition, the transformation of the chalcogenated phenols into diaryl ethers, diarylphenoxathiin, and Gly-T1 inhibitor was demonstrated, by means of the conversion of the remaining hydroxy function.

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology of Japan. We are also grateful for financial support from the foundation of Sanyo broadcasting.

References and Notes

1 a) A. Marcincal-Lefebvre, J. C. Gesquiere, C. Lemer, B. Dupuis, *J. Med. Chem.* **1981**, *24*, 889. b) J. Dumas, D. Brittelli, J. Chen, B. Dixon, H. Hatoum-Mokdad, G. König, R. Sibley, J. Witowsky, S. Wong, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2531. c) G. Liu, J. T. Link, Z. Pei, E. B. Reilly, S. Leitza, B. Nguyen, K. C. Marsh, G. F. Okasinski, T. W. von Geldern, M. Ormes, K. Fowler, M. Gallatin, *J. Med. Chem.* **2000**, *43*, 4025.

2 a) C. W. Nogueira, G. Zeni, J. B. T. Rocha, *Chem. Rev.* **2004**, *104*, 6255. b) G. De Martino, M. C. Edler, G. La Regina, A. Coluccia, M. C. Barbera, D. Barrow, R. I. Nicholson, G. Chiosis, A. Brancale, E. Hamel, M. Artico, R. Silvestri, *J. Med. Chem.* **2006**, *49*, 947. c) B. K. Sarma, G. Mugesh, *Org. Biomol. Chem.* **2008**, *6*, 965.

3 H. B. Glass, E. E. Reid, *J. Am. Chem. Soc.* **1929**, *51*, 3428.

4 A. Van Bierbeek, M. Gingras, *Tetrahedron Lett.* **1998**, *39*, 6283.

5 By Pd catalysts: a) M. Murata, S. L. Buchwald, *Tetrahedron* **2004**, *60*, 7397. b) M. A. Fernández-Rodríguez, Q. Shen, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 2180. By Cu catalysts: c) N. Taniguchi, T. Onami, *J. Org. Chem.* **2004**, *69*, 915. d) S. Kumar, L. Engman, *J. Org. Chem.* **2006**, *71*, 5400. e) D. J. C. Prasad, G. Sekar, *Org. Lett.* **2011**, *13*, 1008. By Co catalyst: f) Y.-C. Wong, T. T. Jayanth, C.-H. Cheng, *Org. Lett.* **2006**, *8*, 5613. By Ni catalyst: g) N. Taniguchi, *J. Org. Chem.* **2004**, *69*, 6904. By La catalyst: h) S. N. Murthy, B. Madhav, V. P. Reddy, Y. V. D. Nageswar, *Eur. J. Org. Chem.* **2009**, 5902. By Mn catalyst: i) M. Bandaru, N. M. Sabbavarpu, R. Katla, V. D. N. Yadavalli, *Chem. Lett.* **2010**, *39*, 1149.

6 a) X.-L. Fang, R.-Y. Tang, P. Zhong, J.-H. Li, *Synthesis* **2009**, 4183. b) J. S. Yadav, B. V. S. Reddy, Y. J. Reddy, K. Praneeth, *Synthesis* **2009**, 1520.

7 a) B. S. Farah, E. E. Gilbert, *J. Org. Chem.* **1963**, *28*, 2807. b) L. Henriksen, *Tetrahedron Lett.* **1994**, *35*, 7057. c) Y. Morita, A. Kashiwagi, K. Nakasuji, *J. Org. Chem.* **1997**, *62*, 7464. d) J. Oddershede, L. Henriksen, S. Larsen, *Org. Biomol. Chem.* **2003**, *1*, 1053. e) I. Sylvestre, J. Wolowska, C. A. Kilner, E. J. L. McInnes, M. A. Halcrow, *Dalton Trans.* **2005**, 3241. f) Y. Kita, T. Takada, S. Mihara, B. A. Whelan, H. Tohma, *J. Org. Chem.* **1995**, *60*, 7144. g) X.-L. Fang, R.-Y. Tang, X.-G. Zhang, J.-H. Li, *Synthesis* **2011**, 1099.

8 D. A. Evans, J. L. Katz, T. R. West, *Tetrahedron Lett.* **1998**, *39*, 2937.

9 a) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz, M. Lemaire, *Chem. Rev.* **2002**, *102*, 1359. b) C.-Y. Gao, L.-M. Yang, *J. Org. Chem.* **2008**, *73*, 1624. c) A. Antoft-Finch, T. Blackburn, V. Snieckus, *J. Am. Chem. Soc.* **2009**, *131*, 17750. d) W. K. Chow, C. M. So, C. P. Lau, F. Y. Kwong, *J. Org. Chem.* **2010**, *75*, 5109. e) G. A. Molander, F. Beaumard, *Org. Lett.* **2010**, *12*, 4022. f) D. A. Wilson, C. J. Wilson, C. Moldoveanu, A.-M. Resmerita, P. Corcoran, L. M. Hoang, B. M. Rosen, V. Percec, *J. Am. Chem. Soc.* **2010**, *132*, 1800.

10 a) A. S. Gybin, W. A. Smit, V. s. Bogdanov, M. Z. Krimer, J. B. Kalyan, *Tetrahedron Lett.* **1980**, *21*, 383. b) M. C. Caserio, C. L. Fisher, J. K. Kim, *J. Org. Chem.* **1985**, *50*, 4390. c) N. Yamagiwa, Y. Suto, Y. Torisawa, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6197.

11 a) M. Wang, K. Ren, L. Wang, *Adv. Synth. Catal.* **2009**, *351*, 1586. b) R. M. Gay, F. Manarin, C. C. Schneider, D. A. Barancelli, M. D. Costa, G. Zeni, *J. Org. Chem.* **2010**, *75*, 5701.

12 At this step, no PhSCl was detected by GC and TLC monitoring.

13 When the last step carried out under argon, the yield of the product decreased to 10%.

14 S. Soloway, S. H. Wilen, *Anal. Chem.* **1952**, *24*, 979.

15 a) B. Feringa, H. Wynberg, *J. Org. Chem.* **1981**, *46*, 2547. b) F. Toda, K. Tanaka, S. Iwata, *J. Org. Chem.* **1989**, *54*, 3007. c) K. Ding, Y. Wang, L. Zhang, Y. Wu, T. Matsuura, *Tetrahedron* **1996**, *52*, 1005. d) M. O. Rasmussen, O. Axelsson, D. Tanner, *Synth. Commun.* **1997**, *27*, 4027. e) K. Ding, Q. Xu, Y. Wang, J. Liu, Z. Yu, B. Du, Y. Wu, H. Koshima, T. Matsuura, *Chem. Commun.* **1997**, 693. f) T.-S. Li, H.-Y. Duan, B.-Z. Li, B. B. Tewari, S.-H. Li, *J. Chem. Soc., Perkin Trans. 1* **1999**, 291. g) K. Wang, M. Lü, A. Yu, X. Zhu, Q. Wang, *J. Org. Chem.* **2009**, *74*, 935.

16 a) D. H. R. Barton, M. Jacob, E. Peralez, *Tetrahedron Lett.* **1999**, *40*, 9201. b) D. Crich, M. Patel, *Tetrahedron* **2006**, *62*, 7824.

17 The reaction of 4-cresol and $(PhSe)_2$ with $FeCl_3$ under argon at 80 °C for 25 h formed the 2-selenylated product in 20% GC yield.

18 T. Kamikawa, T. Hayashi, *Synlett* **1997**, 163.

19 J. Liu, A. E. Fitzgerald, N. S. Mani, *J. Org. Chem.* **2008**, *73*, 2951.

20 G. Smith, G. Mikkelsen, J. Eskildsen, C. Bundgaard, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 3981.

21 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.