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Aluminum(III) Chloride Promoted Oxygen Transfer: Selective Oxidation of Sulfides to Sulfoxides

Yongtao Xie
Yuxin Li
Sha Zhou
Shaa Zhou
Yan Zhang
Minggui Chen
Zhengming Li*

State Key Laboratory of Elemento-Organic Chemistry, Department of Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Weijin Road 94th, Tianjin 300071, P. R. of China
zml@nankal.edu.cn

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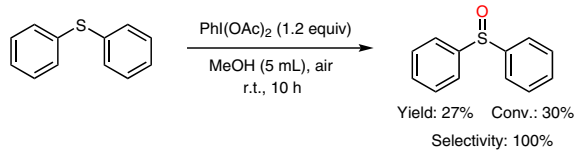
Abstract An efficient selective oxidation of sulfides to sulfoxides has been developed by means of $AlCl_3$-promoted oxygen transfer from phenyliodine diacetate [$PhI(OAc)_2$]. $AlCl_3$ proved to be the optimal Lewis acid for the activation of $PhI(OAc)_2$. Various substituted sulfides were selectively transformed into the corresponding sulfoxides in good to excellent yields (≤99%). The high efficiency, excellent functional-group compatibility, broad substrate scope, and mild conditions render the current transformation useful for the synthesis of sulfoxides.

Key words aluminum trichloride, oxygen transfer, oxidation, sulfides, sulfoxides

Sulfoxide motifs widely exist in natural products, bioactive compounds, medicinal compounds, and other functional molecules.[1] Sulfoxides are also used as chiral ligands and auxiliaries in asymmetric synthesis, because chirality is created at the sulfur atom if its two substituents are not identical.[2] In addition, sulfoxides often play an important role in organic reactions, such as the Swern oxidation,[3] Diels–Alder reaction,[4] and other C–C bond-formation reactions.[5] In light of the importance of sulfoxides, considerable efforts have been devoted toward their preparation by the oxidation of sulfides with various oxidants, including molecular oxygen,[6] hydrogen peroxide or organic hydroperoxides,[7] hypervalent iodine,[8] and other miscellaneous oxidants.[9] However, these procedures have some common limitations, such as overoxidation of the sulfoxides to sulfones; the use of toxic metal catalysts, sensitive or explosive reagents, or high temperatures; the need for laborious workups; and poor functional-group tolerance. Consequently, a mild and easy-to-handle selective oxidation of sulfides to sulfoxides is still highly desired.

Hypervalent iodine compounds have received much attention owing to their versatile oxidizing ability, easy availability, low toxicity, and high stability.[10] Various hypervalent iodine compounds, such as 2-iodoxybenzoic acid and its analogues, have been used in oxidations of sulfides.[11] However, their low solubility in commonly used organic solvents and their potentially explosiveness greatly limit their widespread application in oxidations of sulfides or similar reactions. Hypervalent iodine(III) compounds such as Koser's reagent or Koser's reagent formed in situ from $PhI(OAc)_2$ and TsOH or $NaHSO_4$, are often better alternatives for the oxidation of sulfides.[12]

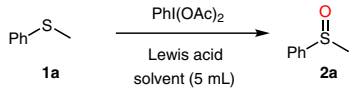
In our previous work, we found that diphenyl sulfoxide was obtained in a 27% yield when diphenyl sulfide was treated with $PhI(OAc)_2$ at room temperature for ten hours (Scheme 1).[13] More importantly, most of the starting material could be recovered, and no overoxidation of the sulfoxide to the sulfone was observed. This result suggested that the use of $PhI(OAc)_2$ as an oxidant might be an attractive approach for the selective oxidation of sulfides to sulfoxides. In addition, we found that Lewis acids are important activators of $PhI(OAc)_2$, and in the case of diphenyl sulfoxide, $BF_3{\cdot}Et_2O$ was the most effective.[14] Here, we report a further modification of that reaction and a highly efficient selective oxidation of sulfides to sulfoxides realized by employing $PhI(OAc)_2$ as the oxidant and $AlCl_3$ as the activator. These transformations featured a high efficiency, excellent functional-group compatibility, a broad substrate scope, and mild conditions. To the best of our knowledge, this is the first time that $AlCl_3$ has been shown to be an efficient activator of $PhI(OAc)_2$.



Scheme 1 Initial discovery

We selected methyl phenyl sulfide (**1a**) as a model substrate to study the reaction (Table 1). In the absence of a Lewis acid additive (entry 1), the desired product **2a** was obtained in 37% yield when $PhI(OAc)_2$ (1.0 equiv) was used as the oxidant in MeOH at room temperature for 12 hours. The addition of $BF_3{\cdot}Et_2O$ or $FeCl_3$, which are particularly efficient in many reactions,[14] did not significantly improve the yield (entries 2 and 3). However, to our surprise, the use of Al_2O_3 greatly improved the yield of **2a** to 66% (entry 4). Further replacement of the Lewis acid additive with $AlCl_3$ further enhanced the yield to 76% (entry 5). With $AlCl_3$ as the optimal Lewis acid, we then examined the effects of a wide range of other solvents for the reaction, all of which gave inferior results to MeOH (entries 6–11). Gratifyingly, however, when a 1:1 mixture of MeCN and MeOH was used, the yield of **2a** was significantly improved to 81% (entry 12). Further investigations of mixed solvents (entries 13–18) showed that a 9:1 mixture of CH_2Cl_2 and MeOH was the optimal solvent, providing **2a** in almost quantitative yield (entry 16). With this optimal solvent, we then examined the optimal loadings of $AlCl_3$ and $PhI(OAc)_2$. A reduction in the $AlCl_3$ loading to 0.3 equivalent led to a significant decrease in the efficiency of the reaction (entry 19), whereas the use of 2.2 equivalents of $PhI(OAc)_2$ shut down the reaction, probably as a result of the functionalization of the methyl group, as indicated by the isolation of (phenylsulfanyl)methyl acetate as a byproduct (entry 20).[15] Notably, when the reaction was performed under an argon atmosphere, a lower yield was obtained (entry 21), suggesting that O_2 benefits this reaction. However, we still did not know the exact reason why this occurs. Therefore, on the basis of the detailed investigations mentioned above, the optimal conditions are as follows: $PhI(OAc)_2$ (1.0 equiv), $AlCl_3$ (0.5 equiv), CH_2Cl_2–MeOH (9:1, 5.0 mL), room temperature, under air.

Table 1 Optimization of the Reaction Conditions[a]

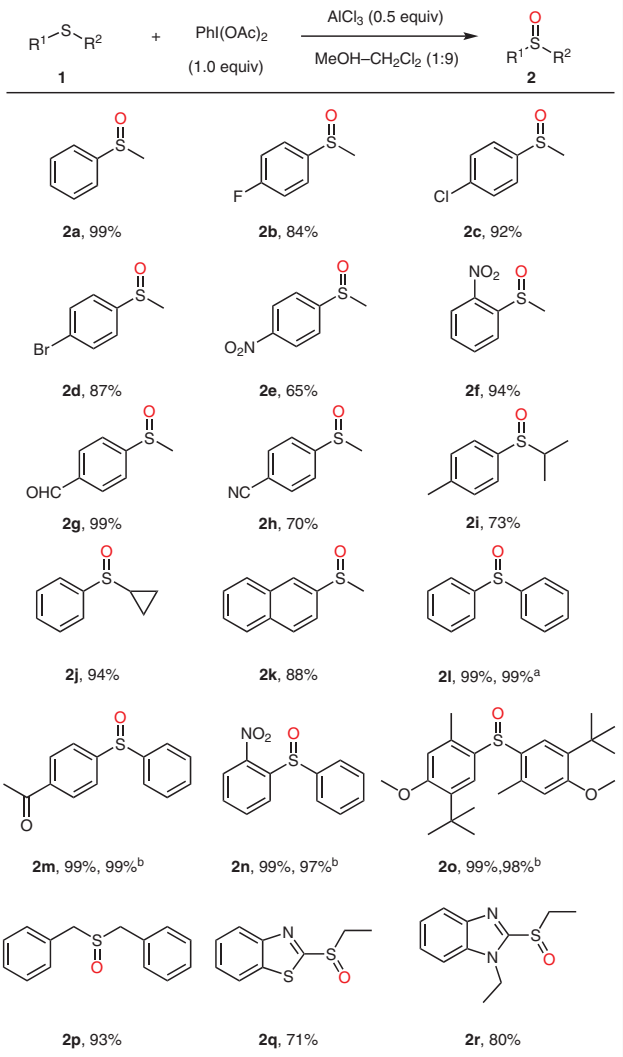


Entry	Lewis Acid (equiv)	Solvent	Yield[b] (%)
1	—	MeOH	37
2	$BF_3{\cdot}Et_2O$ (0.5)	MeOH	30
3	$FeCl_3$ (0.5)	MeOH	24
4	Al_2O_3 (2.0)	MeOH	66
5	$AlCl_3$ (0.5)	MeOH	76
6	$AlCl_3$ (0.5)	EtOH	69
7	$AlCl_3$ (0.5)	*i*-PrOH	56
8	$AlCl_3$ (0.5)	MeCN	11
9	$AlCl_3$ (0.5)	1,4-dioxane	5
10	$AlCl_3$ (0.5)	toluene	26
11	$AlCl_3$ (0.5)	CH_2Cl_2	20
12	$AlCl_3$ (0.5)	MeCN–MeOH (1:1)	81
13	$AlCl_3$ (0.5)	toluene–MeOH (1:1)	83
14	$AlCl_3$ (0.5)	CH_2Cl_2–MeOH (1:1)	88
15	$AlCl_3$ (0.5)	CH_2Cl_2–MeOH (5:1)	96
16	**$AlCl_3$ (0.5)**	**CH_2Cl_2–MeOH (9:1)**	**99**
17	$AlCl_3$ (0.5)	CH_2Cl_2–MeOH (1:5)	78
18	$AlCl_3$ (0.5)	CH_2Cl_2–MeOH (1:9)	71
19	$AlCl_3$ (0.3)	CH_2Cl_2–MeOH (9:1)	56
20	$AlCl_3$ (0.5)	CH_2Cl_2–MeOH (9:1)	0[c]
21	$AlCl_3$ (0.5)	CH_2Cl_2–MeOH (9:1)	84[d]

[a] Reaction conditions: **1a** (1.0 mmol), $PhI(OAc)_2$ (1.0 mmol), solvent (5 mL), r.t., air, 12 h.
[b] Isolated yield.
[c] $PhI(OAc)_2$ (2.2 mmol).
[d] Under argon.

With the optimized conditions in hand, we then set out to investigate the scope of this reaction. As shown in Scheme 2, this reaction displayed high functional-group compatibility, and proved to be a general method for the preparation of sulfoxides. Alkyl aryl sulfides bearing 4-fluoro, 4-chloro, or 4-bromo groups on the aryl ring showed good reactivity, providing the corresponding products **2b–d** in 84–92% yield. Strongly electron-withdrawing substituents such as 2- or 4-nitro (**2e** and **2f**), 4-formyl (**2g**), or 4-cyano (**2h**), were also compatible with the method, and showed no significant decrease in yield. In addition, an electron-donating 4-methyl group on the benzene ring was also tolerated, and the corresponding product **2i**, was obtained in a good yield. Methyl 2-naphthyl sulfide also proved to be good substrate, giving the corresponding sulfoxide **2k** in 88% yield.

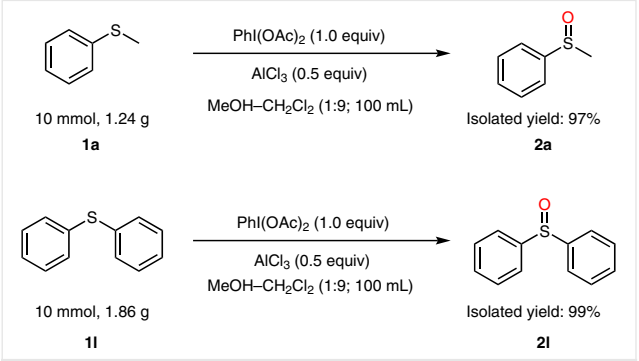
Sulfides containing various alkyl groups with different degrees of steric hindrance also reacted well in this reaction to give products **2f**, **2i**, and **2j**. A series of diaryl sulfides bearing electron-donating or electron-withdrawing groups were also compatible with this reaction, providing the corresponding products **2l–o** in almost quantitative yields. More importantly, lower loadings of $AlCl_3$ (1–5 mol%) could be used for these diaryl sulfides, unlike the case of alkyl-substituted sulfides. We reasoned that the absence in these diaryl sulfides of reactive α-hydride groups, which are present in the alkyl-substituted substrates, suppressed potential side reactions, thereby markedly improving the efficiency of $AlCl_3$. Impressively, a diaryl sulfide with a considerable degree of steric hindrance still gave a high yield of sulfoxide **2o**. Notably, dibenzyl sulfide was also a suitable



Scheme 2 Substrate scope.*Reaction conditions*: Sulfide **1** (1.0 mmol), $PhI(OAc)_2$ (1.0 mmol), $AlCl_3$ (0.5 mmol), 9:1 CH_2Cl_2–MeOH (5.0 mL), r.t., 12 h, under air. Isolated yields are reported.
[a] $AlCl_3$ (0.01 mmol).
[b] $AlCl_3$ (0.05 mmol).

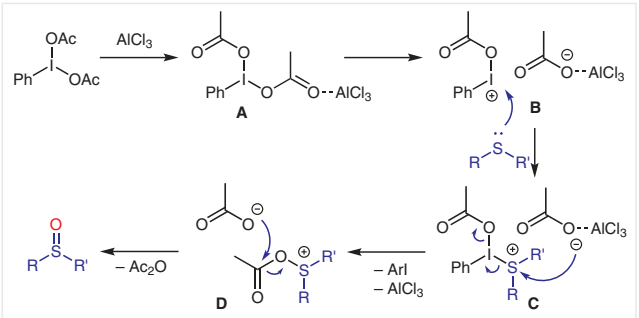
substrate in this reaction, delivering the desired product **2p** in 93% yield. Compared with the previously reported methods,[6–9] the current method showed better compatibility with hetaryl sulfides such as benzothiazolyl (**2q**) or benzimidazolyl (**2r**) sulfides, which holds promise for its widespread application in the synthesis of a broad range of bioactive molecules.

To demonstrate the synthetic utility of our reaction, we conducted two gram-scale reactions (Scheme 3), and sulfoxides **2a** and **2l** were isolated in 97% and 99% yield, respectively, without any notable loss of efficiency.



Scheme 3 Gram-scale reactions

On the basis of our previous work,[13] we propose a plausible mechanism shown in Scheme 4. Initially, $PhI(OAc)_2$ is activated by $AlCl_3$ to give the ion pair **B**, which further reacts with sulfide to form the intermediate **C**. The sulfur atom is then attacked by the nucleophilic oxygen atom of the acetic anion to release $AlCl_3$ and ArI. Finally, intramolecular nucleophilic attack of intermediate **D** leads to the formation of the desired sulfoxide and acetic anhydride.



Scheme 4 Proposed reaction mechanism

In conclusion, a selective oxidation of sulfides to sulfoxide has been realized by an $AlCl_3$-promoted oxygen-transfer pathway.[16] This method provides efficient access to various sulfoxides under mild and easily handled conditions. $AlCl_3$ was found, for the first time, to be an effective activator in the activation of $PhI(OAc)_2$. The formation of alkyl-substituted sulfoxides needed 50 mol% of $AlCl_3$, whereas diaryl sulfoxides required only 1–5 mol% of $AlCl_3$. Additionally, this protocol features good scalability, excellent functional-group compatibility, and a broad substrate scope, which hold promise for its widespread application in the synthesis of sulfoxides.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591496.

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(15) The composition of the byproduct mixture was rather complicated. The main byproduct, (phenylsulfanyl)methyl acetate was isolated in 37% yield.

(16) **Sulfoxides 2; General Procedure**

A 25 mL glass tube was charged with the appropriate sulfide **1** (1 mmol), MeOH (0.5 mL), and CH_2Cl_2 (4.5 mL). $AlCl_3$ (0.5 mmol) was added, and the mixture was stirred at r.t. for 1 min. $PhI(OAc)_2$ (1.0 equiv) was then added and the solution was stirred at r.t. until the sulfide was consumed (TLC). The solvent was removed under reduced pressure and the crude product was purified by column chromatography [silica gel (200–300 mesh), EtOAc–PE].

Methyl Phenyl Sulfoxide (2a)

Colorless oil; yield: 138.6 mg (99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (dd, *J* = 7.8, 1.8 Hz, 2 H), 7.56–7.47 (m, 3 H), 2.72 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 145.33, 130.99, 129.28, 123.41, 43.71. MS (ESI): *m/z* $[M + H]^+$ calcd for C_7H_9OS: 141.0; found: 141.0.

4-Fluorophenyl Methyl Sulfoxide (2b)

Colorless oil; yield: 132.7 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.63 (m, 2 H), 7.28–7.21 (m, 2 H), 2.73 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 165.47, 162.97, 140.94, 125.88, 125.80, 116.73, 116.50, 43.97. MS (ESI): *m/z* $[M + H]^+$ calcd for C_7H_8FOS: 159.0; found: 158.8.

4-Chlorophenyl Methyl Sulfoxide (2c)

Colorless oil; yield: 160.1 mg (92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 8.4 Hz, 2 H), 7.51 (d, *J* = 8.6 Hz, 2 H), 2.72 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.05, 137.06, 129.52, 124.92, 43.84. MS (ESI): *m/z* $[M + H]^+$ calcd for C_7H_8ClOS: 175.0; found: 175.1.

4-Bromophenyl Methyl Sulfoxide (2d)

White solid; yield: 189.7 mg (87%); mp 79–81°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, *J* = 8.5 Hz, 2 H), 7.51 (d, *J* = 8.5 Hz, 2 H), 2.70 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 144.85, 132.58, 125.47, 125.19, 44.00. MS (ESI): *m/z* $[M + H]^+$ calcd for C_7H_8BrOS: 218.9; found: 218.9.