Electronic Supplementary Material (ESI) for ChemComm.

Flavin-catalyzed aerobic oxidation of sulfides and thiols with formic acid / triethylamine

Shun-Ichi Murahashi,*[a] Dazhai Zhang,[a] Hiroki Iida,[b] Toshio Miyawaki,[c] Masaaki Uenaka,[c] Kenji Murano[c] and Kanji Meguro[c]

[a]Department of Chemistry, Okayama University of Science, Ridai-cho, Kita-ku, Okayama, 700-0005 (Japan), [b]Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya, 464-8603 (Japan), [c]CT Laboratory, Hamari Chemicals, Ltd., 1-4-29, Kunijima, Higashiyodogawa-ku, Osaka, 533-0024 (Japan).

murahashi@high.ous.ac.jp

Supporting information

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General Information

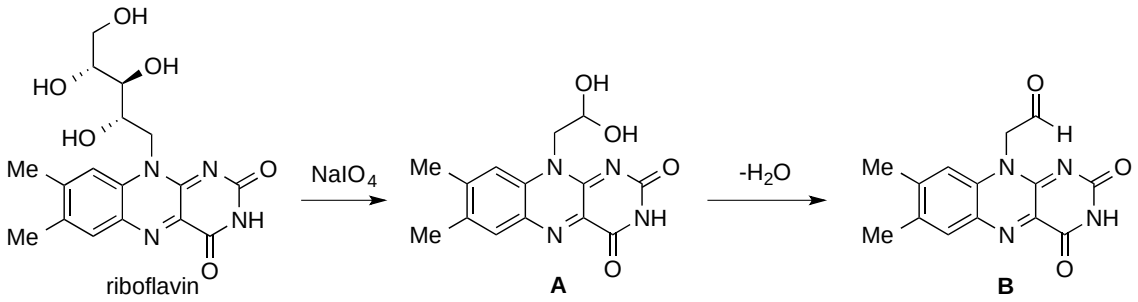
Melting points (M.p.) were determined on METTLER TOLEDO MP70 Melting Point Systems and are uncorrected. The IR spectra were recorded on a JASCO FT/IR-680 spectrophotometer (JASCO, Tokyo, Japan). The NMR spectra were measured using a Varian AS500 spectrometer (Varian, Palo Alto, CA) and a JEOL Lambda 500 spectrometer (JEOL, Akishima, Japan) operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C using tetramethylsilane (TMS) or a solvent residual peak as the internal standard. LC analyses were carried out on MERCK Silica gel 60 F_{254} plates. Chromatographic purification was carried out on silica gel columns (MERCK Silica gel 60 0.040-0.063 mm). Analytical HPLC was conducted on a YMC-Pack Pro C_{18} AS302 column (5 μm, 4.6 x 150 mm i.d.) eluted with 0.1% (v/v) formic acid in acetonitrile (CH_3CN)/water (10%/90%(v/v)) (solvent A) and 0.1% (v/v) formic acid in CH_3CN/water (90%/10% (v/v)) (solvent B), according to the following elution gradient: 0-20 min, 30-80% B at a flow rate of 0.8 mL/min. All starting materials were purchased from Aldrich (Milwaukee, 1 WI), Wako Pure Chemical Industries (Osaka, Japan), or Tokyo Kasei (TCI, Tokyo, Japan) and were used as received.

Preparation of 10-(2,2-dihydroxylethyl)-7,8-dimethylisoalloxazine (A).[1] To a suspension of riboflavin (5.0 g) in water (200 mL) was added sodium periodate (8.0 g). The mixture was stirred at room temperature overnight. The precipitate was filtered, then washed with water, methanol, and ether successively, and dried in vacuum to give 10-(2,2-dihydroxylethyl)-7,8-dimethylisoalloxazine (**A**). ^{1}H NMR in TFA-*d* was consistent with the structure of **A** without any signal of **B** even in high concentration. The product was refluxed in toluene for 4 h. The precipitate was filtered off and washed with ether to give pure 10-(2-oxoethyl)-7,8-dimethylisoallozazine **(B)**, which was confirmed by NMR.

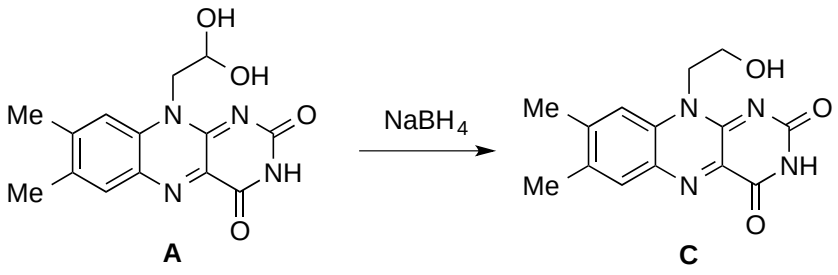
10-(2,2-Dihydroxylethyl)-7,8-dimethylisoalloxazine (A): M.p. 290-293 ^{o}C (decomposed). ^{1}H NMR (500 MHz, TFA-d): δ 8.27 (s,1H, ArH), 7.83 (s, 1H, ArH), 6.94 (dd, 1H, J =2.75, 7 Hz, CH), 5.47 (dd, 1H, *J* =7.3, 14.7 Hz, 1H, CH-Ha), 5.23 (dd, *J* = 2.75, 14.65 Hz, 1H, CH-Hb), 2.68 (s, 3H, CH_3), 2.56 (s, 3H, CH_3). ^{13}C NMR (125 MHz,

TFA-*d*): δ 161.9, 160.9, 148.24, 148.17, 143.5, 143.1, 134.4, 130.6, 130.5, 117.9, 84.5, 60.2, 22.8, 20.7.

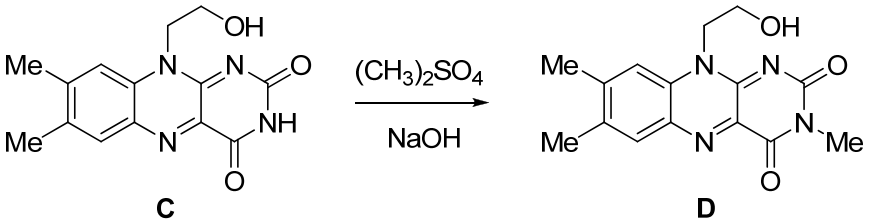
10-(2-Oxoethyl)-7,8-dimethylisoallozazine (B)[1]: ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.40 (s, 1H, NH), 9.72 (s, 1H, CHO), 7.93 (s, 1H, ArH), 7.70 (s, 1H, ArH), 5.63 (s, 2H) 2.44 (s, 3H), 2.38 (s, 3H).



Preparation of 10-(2-hydroxylethyl)-7,8-dimethylisoalloxazine (C). To a suspension of **A** (285 mg, 0.94 mmol) in 100 mL of methanol was added $NaBH_4$ (57 mg, 1.5 mmol). The mixture was stirred at room temperature overnight. The precipitate was filtered off and washed with water, methanol, and ether successively, and dried in vacuum to give **C** (235 mg, 87%). ^{1}H NMR (500 MHz, TFA-*d*): δ 8.15 (s, 1H, ArH), 8.11 (s, 1H, ArH), 5.41 (t, *J*=4.6 Hz, 2H, CH_2O), 4.98 (t, *J*=4.6 Hz, 2H, CH_2N), 2.64 (s, 3H, CH_3), 2.51 (s, 3H, CH_3). ^{13}C NMR (125 MHz, TFA-*d*): δ 161.5, 160.1, 150.9, 147.8, 143.9, 142.1, 134.6, 132.5, 132.3, 118.6, 61.5, 54.0, 23.0, 20.3. HRMS (FAB+): *m/z* calcd for $C_{14}H_{15}N_4O_3$ ($M+H^+$), 287.1139; found, 287.1126.



Preparation of 10-(2-hydroxylethyl)-3,7,8-trimethylisoalloxazine (D). To a suspension of 10-(2-hydroxylethyl)-7,8-dimethylisoalloxazine (**C**) (1.90 g, 6.64 mmol) and dimethyl sulfate (680 uL, 7 mmol) in water (100 mL) was added 1M NaOH aqueous solution (7 mL) dropwise at room temperature. The mixture was stirred for 5 h. The precipitate was filtered off and washed with water, ethanol, and ether successively, and dried in vacuum to give 10-(2-hydroxylethyl)-3,7,8-trimethylisoalloxazine **D** (1.40 g, 70%). M.p.: 275 °C (decomposed). IR (KBr): $\tilde{\nu}$=3423 (m), 1699 (m), 1645 (s), 1583 (s), 1549 (s), 1459 (w), 1280 (w), 1202 (w), 1056 (w), 808 (w), 771 (w) cm^{-1}. ^{1}H NMR (500 MHz, TFA-*d*): δ 8.28 (s, 1H, ArH), 8.19 (s, 1H, ArH), 5.30 (brs, 2H, CH_2O), 4.57 (t, *J*=4.5 Hz, 2H, CH_2N), 3.68 (s, 3H, CH_3), 2.74 (s, 3H, CH_3), 2.63 (s, 3H, CH_3). ^{13}C NMR (125 MHz, TFA-*d*): δ 161.87, 159.75, 151.82, 147.72, 142.52, 142.27, 134.66, 132.41, 132.08, 118.61, 61.53, 53.64, 30.65, 23.00, 20.35. HRMS (FAB+): *m/z* calcd for $C_{15}H_{16}N_4O_3$ ($M+H^+$), 301.1301; found, 301.1302.



C D

Preparation of 5-ethyl-10-(2-hydroxylethyl)-3,7,8-trimethylisoalloxazinium triflate (5d). A mixture of 10-(2-hydroxylethyl)-3,7,8-trimethylisoalloxazine (**D**) (300 mg, 1.0 mmol), 5% Pd-C (42.6 mg, 0.02 mmol), conc. HCl (1.7 mL), and acetaldehyde (1.32 g, 30 mmol) in degassed 95% ethanol (20 mL), and water (20 mL) was stirred overnight under molecular hydrogen. The reaction mixture was filtered through a pad of Celite under argon, giving an orange-brown solution, and most of the solvents were evaporated under reduced pressure. After successive addition of 2 M aqueous HOTf solution (3.0 mL, 6 mmol), $NaNO_2$ (0.345 g, 5.0 mmol), and NaOTf (1.72 g, 10 mmol), the mixture was stirred at room temperature for 15 min. The resulting purple precipitate was collected by filtration, washed with cold water (10 mL) and ether (10 mL x 3), and recrystallized from acetonitrile/ether to give **5d** (351 mg, 73%) as a purple powder. M.p.: 201.1-202.3 °C. UV/Vis (acetonitrile): λ_{max}=224, 286, 417, 559 nm. IR (KBr):

$\tilde{\nu}$=1710 (w), 1655 (m), 1600 (w), 1559 (s), 1459 (w), 1363 (w), 1248 (m), 1163 (w), 1029 (m), 640 (m) cm^{-1}. ^1H NMR (500 MHz, CD_3CN): δ 8.19 (s, 1H, ArH), 8.12 (s, 1H, ArH), 4.96 (br, 4H, CH_2), 4.04 (m, 2H, CH_2), 3.42 (s, 3H, CH_3), 3.29 (t, J = 5.8 Hz, 1H, OH), 2.62 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 1.79 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, CD_3CN): δ 157.01, 153.76, 153.53, 150.44, 143.42, 137.88, 131.10, 127.48, 121.32, 120.06, 58.96, 53.34, 50.75, 30.03, 21.51, 20.27, 15.47. Anal. Calcd for $C_{18}H_{21}F_3N_4O_6S$: C, 45.19; H, 4.42; N, 11.71.Found: C, 45.17; H, 4.42; N, 11.70.

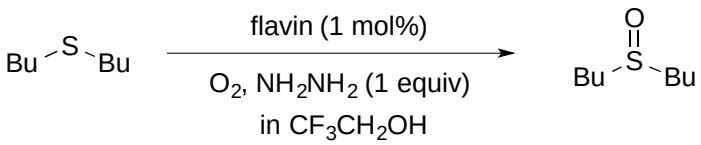
Preparation of 5-ethyl-10-(2-hydroxylethyl)-3,7,8-trimethylisoalloxazinium perchlorate (5e). A mixture of 10-(2-hydroxylethyl)-3,7,8-trimethylisoalloxazine (**D**) (600 mg, 2.0 mmol), 5% Pd-C (850 mg, 0.4 mmol), conc. HCl (3.6 mL), and acetaldehyde (2.9 g, 66 mmol) in degassed 95% ethanol (40 mL), and water (40 mL) was stirred for 48 h under molecular hydrogen. The reaction mixture was filtered through a pad of Celite under argon, and most of the solvents were evaporated under reduced pressure. After successive addition of 2 M aqueous $HClO_4$ solution (9.2 mL, 18.4 mmol), $NaNO_2$ (0.92 g, 13 mmol), and $NaClO_4$ (2.72 g, 22 mmol), the mixture was stirred at room temperature for 2 h. The resulting purple precipitate was collected by filtration, washed with cold water and ether to give **5e** (516 mg, 60%) as a purple powder. M.p.: 169.7-171.2 °C. UV/Vis (acetonitrile): λ_{max}=224, 286, 416, 559 nm. IR (KBr): $\tilde{\nu}$=1710 (w), 1655 (m), 1600 (w), 1559 (s), 1458 (w), 1364 (w), 1120 (m), 1087 (w) cm^{-1}. ^1H NMR (500 MHz, CD_3CN): δ 8.20 (s, 1H, ArH), 8.12 (s, 1H, ArH), 4.95 (br, 4H, CH_2), 4.04 (t, J = 5.3 Hz, 2H, CH_2), 3.42 (s, 3H, CH_3), 3.23 (s, 1H, OH), 2.62 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 1.79 (t, J = 7.3 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, CD_3CN): δ 157.00, 153.74, 153.55, 150.45, 143.39, 137.84, 131.14, 127.49, 121.32, 120.02, 58.99, 53.35, 50.72, 30.022, 30.016, 21.50, 20.27, 15.48. HRMS (FAB+): *m*/*z* calcd for $C_{17}H_{21}N_4O_3$ ($M - ClO_4^-$), 329.1608; found 329.1600.

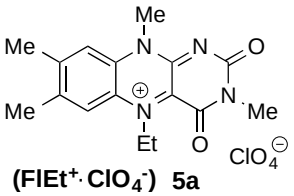
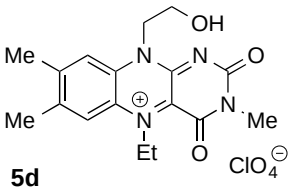
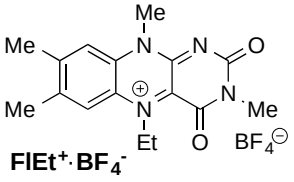
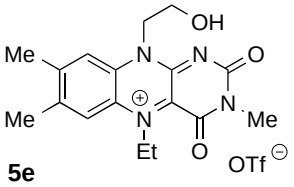
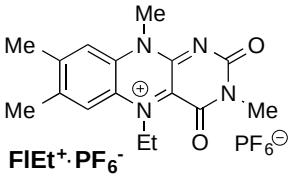
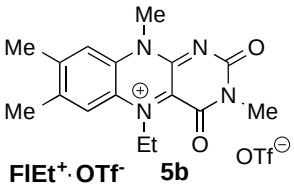
Preparation of 5-ethyl-3,7,8,10-tetramethylisoalloxazinium triflate ($FlEt^+ \cdot OTf^-$) (5b). A mixture of 3,7,8,10-tetramethylisoalloxazine (270 mg, 1.0 mmol), 5% Pd-C (42.6 mg, 0.02 mmol), conc. HCl (1.7 mL), and acetaldehyde (1.32 g, 30 mmol) in degassed 95% ethanol (20 mL), and water (20 mL) was stirred overnight under

molecular hydrogen. The reaction mixture was filtered through a pad of Celite under argon, giving an orange-brown solution, and most of the solvents were evaporated under reduced pressure. After successive addition of 2 M aqueous HOTf solution (3.0 mL, 6 mmol), $NaNO_2$ (0.345 g, 5.0 mmol), and NaOTf (1.72 g, 10 mmol), the mixture was stirred at room temperature for 15 min. The resulting purple precipitate was collected by filtration, washed with cold water (10 mL) and ether (10 mL x 3), and recrystallized from acetonitrile/ether to give **FlEt$^+$·OTf$^-$** (**5b**) (332 mg, 74%) as a purple powder. M.p. 176.4-177.8 °C. UV/Vis (acetonitrile): λ_{max}=221, 285, 413, 557 nm. IR (KBr): $\tilde{\nu}$=1710 (w), 1655 (m), 1603 (w), 1560 (s), 1275 (m), 1255 (m), 1176 (m), 1031 (m), 638 (m) cm^{-1}. ^{1}H NMR (500 MHz, CD_3CN): δ 8.21 (s, 1H, ArH), 7.95 (s, 1H, ArH), 5.01 (br, 2H, CH_2), 4.17 (s, 3H, CH_3), 3.41 (s, 3H, CH_3), 2.63 (s, 3H, CH_3), 2.57 (s, 3H, CH_3), 1.78 (t, J = 7.0 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, CD_3CN): δ 156.98, 154.23, 153.58, 150.74, 143.32, 137.33, 131.29, 127.25, 121.57, 119.20, 53.22, 35.66, 30.00, 21.44, 20.45, 15.55. Anal. Calcd for $C_{17}H_{19}F_3N_4O_5S$: C, 45.53; H, 4.27; N, 12.49. Found: C, 45.44; H, 4.13; N, 12.51.

General procedure for the aerobic oxidation of dibutyl sulfide in the presence of a flavin catalyst and NH_2NH_2 in CF_3CH_2OH. A mixture of dibutyl sulfide (146 mg, 1.0 mmol), flavin catalyst (0.01 mmol), and $NH_2NH_2·H_2O$ (50,1 mg, 1.0 mmol) in CF_3CH_2OH (1.0 mL) was vigorously stirred under molecular oxygen (1atm, balloon) at 35 °C for 3 h. The reaction was quenched with saturated aqueous Na_2SO_3 solution. The yield of sulfoxide was determined by means of ^{1}H NMR analysis. These results are summarized in Table S1.

Table S1 Aerobic Flavin-Catalyzed Oxidation of Dibutylsulfide with NH_2NH_2 in CF_3CH_2OH[a]

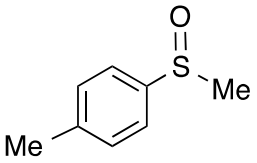


Entry	Flavin catalyst	Yield [%][b]	Entry	Flavin catalyst	Yield [%][b]
1	 **(FlEt$^+$·ClO$_4^-$) 5a**	99	5	 **5d**	97
2	 **FlEt$^+$·BF$_4^-$**	99	6	 **5e**	99
3	 **FlEt$^+$·PF$_6^-$**	91	7	none	none
4	 **FlEt$^+$·OTf$^-$ 5b**	93			

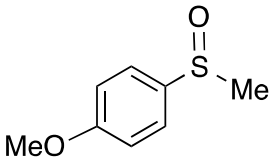
[a] The oxidation of dibutyl sulfide (1 M) was carried out in the presence of flavin catalyst (1 mol%) and $NH_2NH_2·H_2O$ (1.0 equiv) in CF_3CH_2OH at 35 °C for 3 h under O_2 (1 atm). [b] The yield was determined by ^{1}H NMR.

General procedure for the aerobic oxidation of sulfides with formic acid / triethylamine in the presence of 5d catalyst. As typical examples the syntheses of methyl 4-methylphenyl sulfoxide and methyl 4-methoxyphenyl sulfoxide were described. Control experiments showed that the starting materials were recovered, when the aerobic oxidation reactions were carried out without the catalyst **5d**.

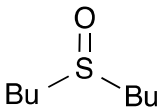
Methyl 4-methylphenyl sulfoxide. To a solution of methyl 4-methylphenyl sulfide (69 mg, 0.5 mmol) in CH_3CN (0.4 mL) were added a formic acid-triethylamine mixture (molar ratio = 8:1) (367 mg, 6.25 mmol as formic acid) and the flavin catalyst **5d** (12 mg, 5 mol%). The reaction mixture was stirred at 60 ºC for 24 h under molecular oxygen (1atm, balloon) and then cooled down to room temperature. Water (10 mL) was added to the reaction mixture, which was extracted with ethyl acetate (10 mL). The organic layer was washed with water (10 mL), a saturated aqueous sodium hydrogen carbonate solution (10 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane-ethyl acetate (2:1 to 1:3) to give methyl 4-methylphenyl sulfoxide as colorless oil (73 mg, 95%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 (d, J = 8.3 Hz, 2H, ArH), 7.35 (d, J = 7.9 Hz, 2H, ArH), 2.71 (s, 3H, CH_3), 2.42 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.54, 141.53, 130.05, 123.56, 44.02, 21.40.



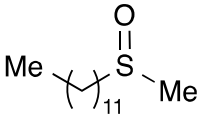
Methyl 4-methoxyphenyl sulfoxide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, J = 9.0 Hz, 2H, ArH), 7.35 (d, J = 8.9 Hz, 2H, ArH), 3.86 (s, 3H, CH_3O), 2.70 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.09, 136.69, 125.58, 114.97, 55.64, 44.09.



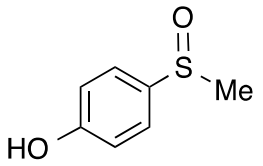
Dibutyl sulfoxide: ^{1}H NMR (50 0 MHz, $CDCl_3$): δ 2.61-2.73 (m, 2H, H), 1.69-1.81 (m, 2H, H), 1.41-1.57 (m, 2H, H), 0.97 (t, J = 7.4 Hz, 3H, H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.22, 24.70, 22.17, 13.77.



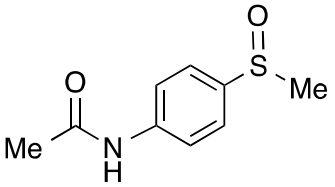
Methyl dodecyl sulfoxide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.62-2.77 (m, 2H, H), 2.56 (s, 3H, H), 1.74-1.81 (m, 2H, H), 1.26-1.51 (m, 18H, H), 0.88 (t, J = 6.9 Hz, 3H, H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 54.95, 38.70, 32.02, 29.72, 29.65, 29.47, 29.45, 29.33, 28.93, 22.80, 22.68, 14.23.



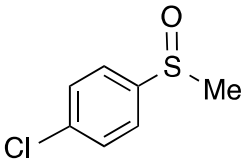
4-Hydroxyphenyl methyl sulfoxide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.8 Hz, 2H, ArH), 6.97 (d, *J* = 8.8 Hz, 2H, ArH), 2.76 (s, 3H, H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.57, 133.64, 126.22, 116.94, 43.26.



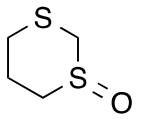
4-Acetoamidephenyl methyl sulfoxide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.40 (bs, 1H, NH), 7.71 (d, *J* = 8.6 Hz, 2H, ArH), 7.57 (d, *J* = 8.7 Hz, 2H, ArH), 2.73 (s, 3H, H), 2.19 (s, 3H, H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.18, 141.35, 139.64, 124.79, 120.49, 43.97, 24.68.



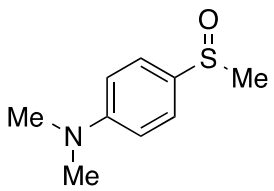
4-Chlorophenyl methyl sulfoxide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.60 (d, *J* = 8.6 Hz, 2H), 7.52 (d, *J* = 8.7 Hz, 2H), 2.72 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.35, 137.39, 129.78, 125.09, 44.16.



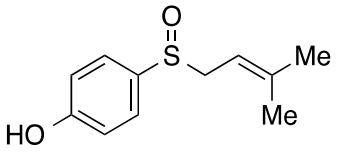
1,3-Dithiane 1-oxide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.01 (d, *J* = 12.4 Hz, 1H, H), 3.65 (d, *J* = 12.7 Hz, 1H, H), 3.31-3.36 (m, 1H, H), 2.48-2.69 (m, 4H, H), 2.17-2.27 (m, 1H, H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 52.98, 50.54, 28.40, 27.25.



***N*,*N*-Dimethyl-4-(methylsulfinyl)aniline:** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (d, *J* = 9.0 Hz, 2H, ArH), 6.76 (d, *J* = 9.0 Hz, 2H, ArH), 3.02 (s, 6H, $(CH_3)_2N$), 2.69 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.6, 130.5, 125.6, 112.2, 43.8, 40.3.

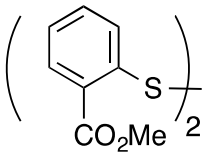


4-[(3-Methylbut-2-en-1-yl)sulfinyl]phenol: ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.10 (brs, 1H, ArOH), 7.45-7.42 (m, 2H, ArH), 6.98-6.95 (m, 2H, ArH), 5.03-5.00 (m, 1H, CH=C), 3.69-3.64 (m, 1H, either H of CH_2SO), 3.56-3.52 (m, 1H, the other H of CH_2SO), 1.70 (s, 3H, CH_3), 1.44 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.7, 143.0, 131.1, 126.9, 116.6, 110.8, 56.3, 26.0, 18.2.

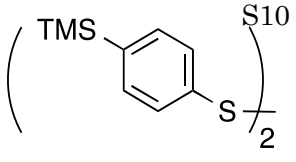


General procedure for the aerobic oxidation of thiols with formic acid / triethylamine in the presence of 5d catalyst. As a typical example the synthesis of bis[2-(methoxycarbonyl)phenyl] disulfide was described. Control experiments showed that the starting materials were recovered, when the aerobic oxidation reactions were carried out without the catalyst **5d.**

Bis[2-(methoxycarbonyl)phenyl] disulfide. To a solution of methylthiosalicylate (84 mg, 0.5 mmol) in CH_3CN (0.4 mL) were added a formic acid-triethylamine mixture (molar ratio = 8:1) (367 mg, 6.25 mmol as formic acid) and the flavin catalyst **5d** (12 mg, 5 mol%). The reaction mixture was stirred at 60 ºC for 4 h under molecular oxygen (1atm, balloon) and then cooled down to room temperature. A saturated aqueous sodium hydrogen carbonate solution (10 mL) was added to the reaction mixture, which was extracted with ethyl acetate (10 mL). The organic layer was washed with a saturated aqueous sodium chloride solution (10 mL), dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel eluting with hexane-ethyl acetate (4:1) to give bis[2-(methoxycarbonyl)phenyl] disulfide as a white solid (78 mg, 93%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J = 7.65 Hz, 2 H, ArH x 2), 7.76 (d, J = 8.25 Hz, 2 H, ArH x 2), 7.41 (t, J = 7.30 Hz, 2 H, ArH x 2), 7.34 (t, J = 7.90 Hz, 2 H, ArH x 2), 3.99 (s, 6 H, CH_3 x 2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.91, 140.34, 133.09, 131.45, 127.23, 125.80, 125.47, 52.41.

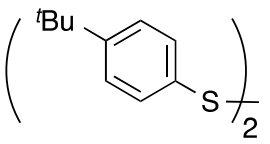


Bis(4-(trimethylsilyl)phenyl) disulfide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.43-7.49 (m,

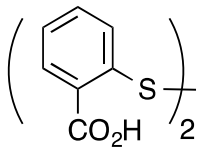


8 H) , 0.24 (s, 19 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.13, 137.79, 133.97, 126.15, -1.18.

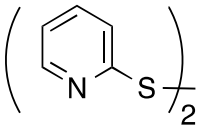
Bis(4-(*tert*-butyl)phenyl) disulfide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.85 Hz, 4 H), 7.32 (d, *J* = 8.55 Hz, 4 H), 1.29 (s, 18 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.43, 133.97, 127.67, 126.10, 34.52, 31.25.



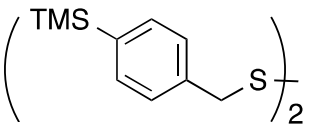
Bis(2-carboxyphenyl) disulfide: ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.60 (bs, 2 H), 8.04 (d, *J* = 7.65 Hz, 2 H), 7.62 (d, *J* = 7.95 Hz, 2 H), 7.57 (t, *J* = 7.95 Hz, 2 H), 7.35 (t, *J* = 7.35 Hz, 2 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 167.63, 138.95, 133.32, 131.62, 128.09, 126.01, 124.99.



Bis(2-pyridyl) disulfide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.46 - 8.47 (m, 2 H), 7.59-7.62 (m, 4 H), 7.10-7.13 (m, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.81, 149.48, 137.34, 121.04, 119. 56.

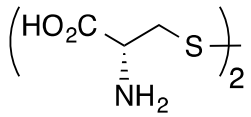


Bis(4-(trimethylsilyl)benzyl) disulfide: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 7.90 Hz, 4 H), 7.22 (d, *J* = 7.95 Hz, 4 H), 3.60 (s, 4 H), 0.26 (s, 18 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.60, 137.72, 133.48, 128.74, 43.22, -1.14.

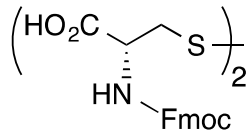


Cystine: ^{1}H NMR (500 MHz, D_2O/CF_3COOD): δ 4.05-4.07 (m, 2 H), 2.30-3.03 (m, 2

H), 2.83-2.87 (m, 2 H). ^{13}C NMR (125 MHz, D_2O/CF_3COOD): δ 170.87, 52.13, 36.61.



Synthesis of *N*,*N*'-bis[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-cystine (14). To a mixture of *S*-[(acetylamino)methyl]-*N*-[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-cysteine (**13**)[2] (207 mg, 0.5 mmol) in CH_3CN (1.5 mL) were added a formic acid-triethylamine mixture (molar ratio = 8:1) (367 mg, 6.25 mmol as formic acid) and the flavin catalyst **5d** (24 mg, 10 mol%). The reaction mixture was stirred at 60 ºC for 20 h under molecular oxygen (1atm, balloon). The clear homogeneous solution obtained was cooled down to room temperature. To the solution were added water (10 mL) and ethyl acetate (10 mL). After separation, the aqueous layer was extracted with ethyl acetate (10 mL). The combined organic layers were extracted with a saturated aqueous sodium hydrogen carbonate solution twice (15 mL x 2). The combined aqueous layers were washed with ethyl acetate twice (10 mL x 2), adjusted with 1N hydrochloric acid to pH 2 and extracted with ethyl acetate twice (15 mL x 2). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under reduced pressure to give *N*,*N*'-bis[(9*H*-fluoren-9-ylmethoxy)carbonyl]-L-cystine (**14**), which was crystallized from ethyl acetate, filtered, washed with a mixed solvent of ethyl acetate and diethyl ether, and dried under reduced pressure for 4h in 84% yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ12.96 (brs, 2H, CO_2H x 2), 7.88 (d, J = 7.5 Hz, 4H, ArH x 4), 7.80 (d, J = 8.0 Hz, 2H, ArH x 2), 7.75-7.60 (m, 2H, NH x 2), 7.70 (dd, J = 7.5, 3.5 Hz, 2H, ArH x 2), 7.40 (td, J = 7.5, 3.5 Hz, 4H, ArH x 4), 7.31 (t, J = 7.5 Hz, 4H, ArH x 4), 4.35-4.15 (m, 8H, $CHCH_2O$ of Fmoc x 2, αH x 2), 3.16 (dd, J = 14.0, 4.0 Hz, 2H, βH x 2) 2.95 (dd, J = 14.0, 10.5 Hz, 2H, βH x 2). ^{13}C NMR (125 MHz, DMSO-d_6): δ172.2, 156.0, 143.8, 143.7, 140.7, 140.7, 127.6, 127.1, 125.3, 125.2, 120.1, 65.7, 52.9, 46.6, one signal overlapped with solvent signal.



Control experiment showed that the starting compound **13** was

recovered, when the aerobic oxidation reaction of **13** was carried out without the catalyst **5d.**

References

1 F. Albericio, A. Grandas, A. Porta and E. Pedroso, *Synthesis,* 1987, 271.

2 J. Svoboda, B. König, K. Sadeghian and M. Schütz, *Verlag Zeitschrift Naturforschung,* 2008, 47.