A practical improvement of odorless Corey–Kim and Swern oxidations†

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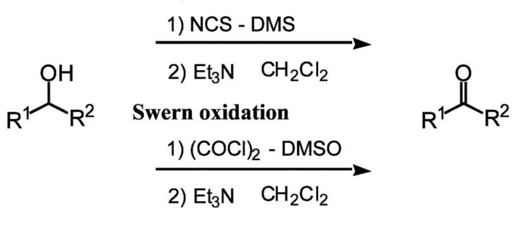
Methyl 6-morpholinohexyl sulfide (**3a**, MMS) and methyl 6-morpholinohexyl sulfoxide (**7**, MMSO) have been employed as efficient odorless substitutes for dimethyl sulfide (DMS) and dimethyl sulfoxide (DMSO) in Corey–Kim and Swern oxidations, respectively. The oxidation products and the byproduct **3a** are easily separable by simple aqueous extraction. The Corey–Kim oxidation was studied in various solvents. The utility of the odorless 6-morpholinohexan-1-thiol (**2a**) in the dealkylation of phenyl ethers and methyl esters is also presented.

Introduction

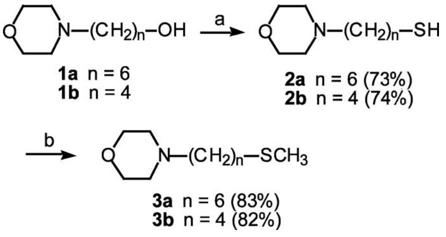
Thiols and sulfides are synthetically versatile functional groups.[1] They are essential reagents in making everything from coatings to pharmaceuticals to catalysts. However, they often have an unbearable and persistent stench. Working with thiol and sulfide reagents can be a very unpleasant experience, especially for those carrying out large-scale, industrial processes. Therefore, we designed a program to prepare odorless variants of the most common malodorous reagents such as ethanethiol, benzenethiol, benzyl mercaptan and dimethyl sulfide (DMS).[2–4] While studying the odor activity of alkane thiols[3] and sulfides (see Tables 1 and 2 in the ESI†), we observed that dodecanethiol and dodecyl methyl sulfide had no odor and thus could be used as odorless substitutes for ethanethiol and DMS, respectively. Prompted by the presidential recognition[5] of innovative syntheses, process improvements and new products that minimize or prevent pollution, chemical industries and academic groups are using the "green" approach to many fundamental synthetic transformations. For instance, in the oxidation of alcohols to aldehydes and ketones, the methods and reagents are constantly being refined and improved, and the largely metal based oxidations[6] are gradually being replaced with better, more efficient catalytic processes.[7] However, completely metal free conditions are of particular importance.[8] The Corey–Kim[9] [*N*-chlorosuccinimide (NCS)–DMS] and Swern[10] [$(COCl)_2$–DMSO] oxidations, which readily convert primary and secondary alcohols to aldehydes and ketones, have harmful environmental implications because both involve DMS either as a reagent (Corey–Kim) or as a byproduct (Swern).



Owing to the immense popularity of these oxidations, the Vederas group pioneered[11] the introduction of polymer supported and extractable reagents.[12] Crich and Neelamkavil addressed this issue using the fluorous extraction method,[13] and we have replaced DMS and DMSO with odorless dodecyl methyl sulfide and the corresponding sulfoxide.[14] However, the laborious separation of dodecyl methyl sulfide after the reaction led us to try to further improve upon the odorless Corey–Kim and Swern oxidations. Here, we present easy to prepare, inexpensive and recyclable amino sulfur reagents, which prove to be better alternatives to the commonly used thiols and sulfides. We discuss the versatility of these sulfur reagents in the Corey–Kim and Swern oxidations and also in dealkylation.

Results and discussion

The thiol **2a** was easily obtained in two steps by condensation of morpholine and commercially available 1-chloro-6-hexanol to give 6-morpholinohexan-1-ol (**1a**) in quantitative yield (>97%), followed by direct thiolation (Scheme 1) using thiourea and HBr *via* the isothiouronium salt.[15] In order to have a relatively 'atom-economical' reagent, the 4-morpholinobutan-1-thiol (**2b**) was prepared in a similar manner from the alcohol **1b**.[16] The thiols **2** could be alkylated selectively using methyl iodide in aqueous alkali medium to give the corresponding methyl sulfides **3**.



Scheme 1 (a) Thiourea, H_2O, 48% HBr, 120 °C, 8 h then 40% NaOH, 120 °C, 2 h; (b) 50% NaOH, EtOH, CH_3I, rt, 3 h.

Following the above procedure, the corresponding 3- and 5-carbon linked morpholino thiols were also prepared to check their relative odor profile (Table 1). The most malodorous in this group, the 3-morpholinopropan-1-thiol (entry 1 in Table 1), is indexed as 3, and the odorless 6-morpholinohexan-1-thiol, 0. The following data further support our earlier observation[3] that the foul smell of thiols on the human olfactory sense is closely related to the length of the carbon chain.

Our initial studies were aimed at the application of the morpholino methyl sulfides **3** as DMS equivalents in the Corey–Kim oxidation using various solvents (Table 2). For such oxidations, THF and acetonitrile as reaction solvents were as good as the commonly used toluene and dichloromethane, whereas ethyl acetate and acetone were ineffective. The reaction in the latter two

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† Electronic supplementary information (ESI) available: experimental procedures and analytical data for other new compounds as well as copies of NMR spectra. See http://www.rsc.org/suppdata/gc/b3/b312849k/

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Table 1 Relative odor scale of morpholinoalkanethiols

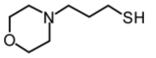
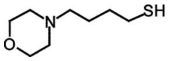
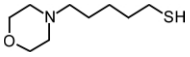
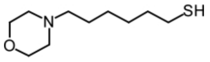
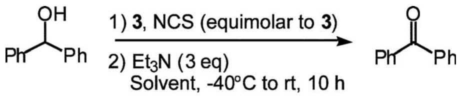
Entry	Thiol	Odor scale
1		3
2		2
3		1
4		0

Table 2 Screening of solvents and stoichiometry

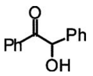
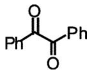
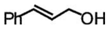
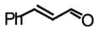
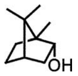
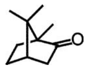
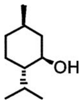
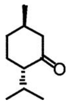
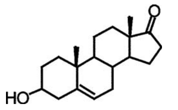
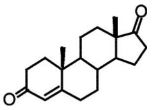
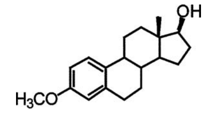
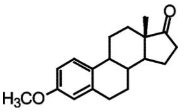
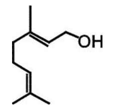
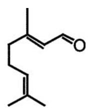


Entry	3/equiv.	Solvent	Yield (%)
1	1.5[a]	Toluene	90
2	2[b]	Toluene	97
3	1.5[a,b]	CH_2Cl_2	96
4	1.5[a]	CH_3CN	91
5	2[b]	CH_3CN	93
6	2[a]	THF	92
7	1.5[a]	AcOEt	16[c]
8	1.5[a]	Acetone	10[c]

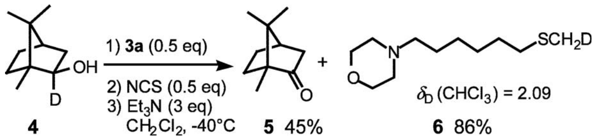
[a] Using **3a**. [b] Using **3b**. [c] NMR yield.

Table 3 Corey–Kim oxidations using **3a**

$$\text{alcohol} \xrightarrow[\text{2) NEt}_3\text{ (3 eq), CH}_2\text{Cl}_2\text{, }-40°\text{C to rt}]{\text{1) }\mathbf{3a}\text{ (1.5 eq), NCS (1.5 eq)}} \text{aldehyde or ketone}$$

Entry	Substrate	Product	Yield (%)	Recd **3a** yield (%)
1			98, 94[a]	81
2			96, 90[b]	81
3			94, 90[a]	89
4			89, 85[c]	74[c]
5			91	77
6			99[c]	70
7			85, 89[c]	82

[a] Reaction performed in CH_3CN using 2 equiv. of reagents. [b] Reaction performed in CH_3CN. [c] Reaction performed in CH_3CN using 2.5 equiv. of reagents.



Scheme 2 A deuterio experiment of the Corey–Kim oxidation using **3a**.

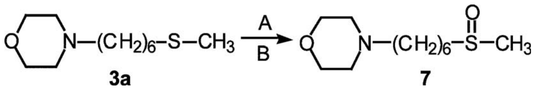
solvent systems looked turbid, apparently suggesting low solubility of the intermediate ylide probably due to the interaction between basic nitrogen on morpholine and carbonyl groups in these solvents, hence resulting in low yields. Most significantly, only 1.5 equivalents of the reagents **3** were enough for the complete conversion of benzhydrol to benzophenone in high isolated yield (96% with 86% recovery of reagent **3**; entry 3, Table 2). The use of a near stoichiometric reagent is important in order to achieve high recovery of **3** after the reaction, since any excess NCS is capable of oxidizing the remaining sulfide. While both of the sulfides **3a** and **3b** have been shown to be efficient alternatives to DMS in preliminary Corey–Kim oxidations, we chose **3a** because the corresponding thiol **2a** is odorless (Table 1).

In order to further test the practicality of the sulfide **3a**,[17] several non-natural and naturally occurring alcohols were subjected to the standard Corey–Kim oxidation (Table 3). The reaction mixture after acidic (1 N HCl) work-up, followed by washing with water and brine, afforded the corresponding crude aldehydes and ketones (>95% pure based on NMR) in very high yields with complete consumption of the starting alcohols. No foul smell was detected and the use of column chromatography was unnecessary. Moreover, the sulfide reagent **3a** could be recycled easily upon basification (pH = 10) using aq. NaOH followed by ethereal extraction. The recovered crude material was distilled (Kuegelruhr; 145 °C, 1.5 mmHg) to obtain the pure sulfide **3a** in high yields (70–90%).

Next we investigated the deuterium transfer experiment of the Corey–Kim oxidation using 2-deuterioisoborneol (**4**). Following the standard protocol, oxidation of **4** (1 equiv.) using **3a** and NCS (0.5 equiv. each) afforded camphor **5** (45%) and sulfide **6** (86%) after acid–base extraction (Scheme 2). Various spectral analyses, including ^2H NMR ($CHCl_3$) with $CDCl_3$ as the reference, confirmed selective deprotonation of the *S*-methyl group (95%) rather than the *S*-methylene group (5%) in **3a**.

Encouraged by the excellent results of the Corey–Kim oxidation, we extended our approach to the more popular Swern oxidation, which employs the corresponding sulfoxide. In order to oxidize the morpholino methyl sulfide **3a**, we had to selectively oxidize the sulfide moiety rather than promote *N*-oxide formation. After several experiments with different reagents and conditions, we discovered that, in order to avoid unwanted *N*-oxidation as well as overoxidation of the sulfide, the best conditions (86% yield) turned out to be *m*-chloroperbenzoic acid (*m*-CPBA, 1.2 equiv.) at −60 °C for 30 min followed by 10 min at 0 °C.

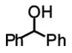
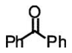
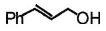
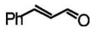
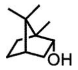
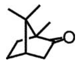
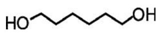
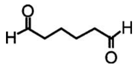
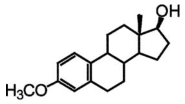
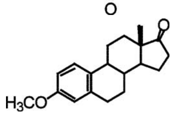
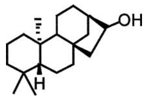
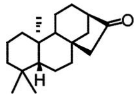
In another attempt to control *N*-oxidation, addition of 1 equivalent of CH_3COX ($X = Br, Cl$) prior to *m*-CPBA also worked very well, providing more than 95% yield of the desired sulfoxide **7** (Scheme 3). Due to its high boiling range (over 180 °C at 1.5 mmHg), **7** was purified by passing it through a short silica gel column. Because of its hygroscopic nature, the sulfoxide **7** requires drying under Dean–Stark conditions for several hours before the Swern oxidation. Following the standard Swern protocol, but using the sulfoxide **7** as a DMSO equivalent, primary and secondary alcohols were oxidized to the corresponding aldehydes and ketones in very high yields (Table 4). In some cases, we found that using 2 equivalents of the sulfoxide **7** and 1.5 equivalents of oxalyl chloride



Scheme 3 *Method A*: *m*-CPBA (1.2 equiv.), $CHCl_3$, −60 °C (30 min), 0 °C (10 min), 86%; *Method B*: CH_3COCl (1 equiv.), *m*-CPBA (1.2 equiv.), $CHCl_3$, −60 °C (30 min), 0 °C (10 min), 95.5%.

Table 4 Swern oxidations using **7**

$$\text{alcohol} \xrightarrow[\text{2) NEt}_3\text{ (3–6 eq), CH}_2\text{Cl}_2\text{, }-60\text{°C to rt}]{\text{1) }\mathbf{7}\text{ (2–3 eq), (COCl)}_2\text{ (1.5–2.5 eq)}} \text{aldehyde or ketone}$$

Entry	Substrate	Product	Yield (%)	Recd **3a** yield (%)
1[a]			94	84
2[a]			94	87
3[a]			92	81
4[b]			91	76
5[a]			96	90
6[a]			95	83

[a] **7**, $(COCl)_2$, Et_3N (2, 1.5, and 3 equiv., respectively). [b] **7**, $(COCl)_2$, Et_3N (3, 2.5, and 6 equiv., respectively).

was necessary to avoid formation of the corresponding chloride. In the case of 1,6-hexanediol (entry 4 in Table 4), 3 equivalents of the sulfoxide **7** and 2.5 equivalents of oxalyl chloride were used for an optimum yield of 91%. In all cases, we employed the acid–base extraction principle to separate the products and to recover the sulfide **3a** so that it could be oxidized back to the sulfoxide **7**.

Next, we examined the utility of the modified odorless thiol **2a** in thiolate anion induced dealkylation reactions. Several phenyl ethers and methyl esters were subjected to dealkylation in the presence of the sodium salt of **2a** (5 equiv.) under the reaction conditions described in Table 5. Although the yields of the products varied, compared to the inherently toxic and malodorous ethanethiol, our reagent **2a** could nonetheless be quite useful because it is odorless and can be reused.

Conclusion

We have demonstrated the use of these modified, sulfur reagents **3a** (MMS) and **7** (MMSO) as odorless alternatives to DMS and DMSO in the Corey–Kim and the Swern oxidations, respectively. The morpholine based thiol **2a** could also act as an odorless alternative to the foul smelling ethanethiol commonly used in industrial settings. The products of these reactions can be easily purified using only acid–base extraction, thereby eliminating unpleasant odors, saving time and protecting the environment. In view of current environmental and economic factors, the utility of these simple reagents could be enormously beneficial.

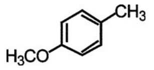
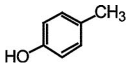
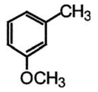
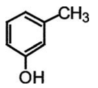
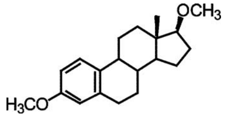
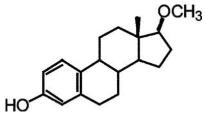
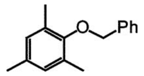
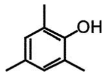
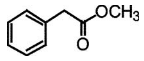
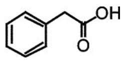
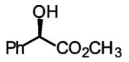
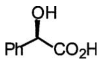
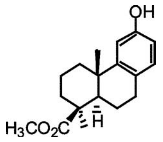
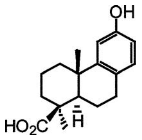
Experimental

General

All reagents were purchased from commercial sources and used as received. All reactions were performed under a dry N_2 atmosphere unless otherwise indicated. Reaction solvents such as toluene, CH_2Cl_2, acetone, acetonitrile, ethyl acetate and DMF were dried prior to use. Analytical TLC was done on precoated (0.25 mm) silica gel plates. Column chromatography was conducted with 230–400 mesh silica gel. Infrared (IR) spectra were measured on a FTIR spectrometer. The ^{2}H NMR (62 MHz) spectrum was recorded in chloroform using $CDCl_3$ (7.26 ppm) as the internal standard. All oxidation and dealkylation substrates were commercially available or prepared by known procedures and used as such and the products were identical to commercial samples.

Table 5 Dealkylation reactions using **2a**

$$\text{phenyl ether or ester} \xrightarrow[\text{DMF, 120°C, 3 h}]{\mathbf{2a}\text{ (5 eq), NaH (6 eq)}} \text{phenolic alcohol or acid}$$

Entry	Reactants	Product	Yield (%)
1[a]			77
2[a]			81
3[a]			72
4[a]			83
5			92
6[b]			92
7[b]			97

[a] Some starting material also recovered. [b] Reaction time, 2 h.

Typical procedure for the preparation of methyl 6-morpholinohexyl sulfide (3a)

To a solution of thiol **2a** (8.34 g, 41.04 mmol) in ethanol (15 mL) was added 50% aqueous NaOH (30 mL). The solution was cooled to 5 °C and MeI (3.83 mL, 61.56 mmol) was added dropwise with stirring. The reaction mixture was stirred at ambient temperature for 3 h. Excess ethanol was distilled off under reduced pressure, the solution diluted with water (100 mL) and extracted with diethyl ether (5×75 mL), washed with brine and dried (Na_2SO_4) and concentrated. The crude colorless oil was distilled at 145 °C/1.5 mmHg to give pure sulfide **3a** (7.4 g, 83%): bp 145 °C (1.5 mmHg); IR ($CHCl_3$): 3030, 2930, 2860, 2815, 2485, 1600, 1460, 1310 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.71 (t, J = 4.6 Hz, 4H), 2.48 (t, J = 6.8 Hz, 2H), 2.42 (br s, 4H), 2.30 (dd, J = 7.1, 2.0 Hz, 2H), 2.08 (s, 3H), 1.52–1.28 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.9, 59.1, 53.8, 34.2, 29.1, 28.7, 27.1, 26.5, 15.6; MS (EI) *m/z* 217 (M$^+$, 3.4), 202 (20), 170 (100), 156 (9.4), 100 (98.1), 87 (19.2); HRMS calcd for $C_{11}H_{23}NOS$: 217.1503, found 217.1500.

Methyl 6-morpholinobutyl sulfide (3b)

Methyl 6-morpholinobutyl sulfide (**3b**) was prepared similarly from **2b** (6.90 g, 39.36 mmol) and MeI (3.67 mL, 59.04 mmol) in 82% yield (6.10 g) as colorless oil: IR ($CHCl_3$): 3005, 2920, 2860, 2815, 2480, 1600, 1460, 1360 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (t, J = 4.7 Hz, 4H), 2.50 (t, J = 7.1 Hz, 2H), 2.42 (br dd, J = 4.4, 4.0 Hz, 4H), 2.34 (t, J = 7.7 Hz, 2H), 2.08 (s, 3H), 1.69–1.52 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.5, 58.1, 53.4, 33.7, 26.5, 25.2, 15.1; MS (EI) *m/z* 189 (M$^+$, 12.8), 142 (16.8), 100 (100), 156 (9.4), 100 (98.1), 83 (22.5); HRMS calcd for $C_9H_{19}NOS$: 189.1184, found 189.1187.

General procedure for the Corey–Kim oxidation using 3a

To a solution of *N*-chlorosuccinimide (63.76 mg, 0.48 mmol) in anhydrous dichloromethane (2 mL) under N_2 at −40 °C was added **3a** (104 mg, 0.48 mmol) in dichloromethane (2 mL) dropwise. The reaction mixture was stirred at −40 °C for 30 min before the addition of the alcohol (0.32 mmol) in dichloromethane (2 mL). After the reaction had been stirred for 2 h at −40 °C, freshly distilled Et_3N (0.14 mL, 0.95 mmol) was added and the reaction mixture was stirred at the same temperature for a further period of 2.5 h. It was then allowed to warm to rt for 8 h with continued stirring before being poured into aq. 1 N HCl (60 mL) and extracted with ethyl acetate (3 × 30 mL). The organic component was washed again with aq. 1 N HCl (50 mL), brine and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to afford the pure aldehyde or ketone.

General procedure for the recovery of 3a

The aq. 1 N HCl solution collected after work-up of Corey–Kim/Swern oxidation was made alkaline (pH > 9) using aq. 5 M NaOH and extracted with diethyl ether (3 × 30 mL), dried (Na_2SO_4) and concentrated followed by Kuegelruhr distillation (145 °C, 1.5 mmHg) to afford the pure **3a**.

Procedure for the synthesis of methyl 6-morpholinohexyl sulfoxide (7) using *m*-CPBA

Method A. To a stirred solution of the sulfide **3a** (518 mg, 2.39 mmol) in chloroform (10 mL) at −60 °C was added *m*-CPBA (642 mg from 77% *m*-CPBA, 2.86 mmol) in portions. The reaction mixture was stirred for 30 min followed by stirring at 0 °C (10 min). It was then quenched and washed with aq. sat. $NaHCO_3$, extracted with $CHCl_3$ and dried (Na_2SO_4). Purification of the crude sulfoxide by a short silica gel column using chloroform and methanol (10 : 1) as eluents afforded the title compound (482 mg, 86%) as a colorless oil.

Method B. To a stirred solution of the sulfide **3a** (1.46 g, 6.74 mmol) in chloroform (20 mL) at ambient temperature was added acetyl chloride (0.5 mL, 6.75 mmol). The reaction mixture was cooled to −60 °C and *m*-CPBA (1.81 g from 77% *m*-CPBA, 8.09 mmol) was added in portions. The reaction mixture was stirred for 30 min followed by warming to 0 °C (10 min). It was then quenched and washed with aq. $NaHCO_3$, extracted with $CHCl_3$ and dried (Na_2SO_4).The crude sulfoxide was purified by a short silica gel column using chloroform and methanol (10 : 1) as eluents to afford **7** (1.50 g, 95.5%): IR ($CHCl_3$): 3030, 2940, 2815, 2475, 1600, 1460, 1425, 1305 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 3.72 (t, J = 4.6 Hz, 4H), 2.74–2.62 (m, 2H), 2.57 (s, 3H), 2.44 (br s, 4H), 2.33 (dd, J = 7.3, 0.6 Hz, 2H), 1.78 (quint, J = 7.7 Hz, 2H), 1.56–1.34 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 66.9, 58.9, 54.6, 53.7, 38.5, 28.7, 27.1, 26.3, 22.5; MS (FAB) *m/z* 234 (M^++1, 100), 216 (15), 170 (25), 147 (20), 100 (45); HRMS calcd for $C_{11}H_{23}NO_2S$ (M^++H): 234.1540, found 234.1525.

General procedure for the Swern oxidation using 7

To a well-stirred solution of anhydrous CH_2Cl_2 (5 mL) under dry N_2 atmosphere at −60 °C was added oxalyl chloride (20.5 μL, 0.24 mmol). A solution of **7** (73.25 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) was then added dropwise and the reaction mixture was stirred for an additional 20 min. The alcohol (0.16 mmol) dissolved in CH_2Cl_2 (2 mL) was added to this solution followed, after an additional 30 min to 1 h, by freshly distilled Et_3N (66 μL, 0.48 mmol). The reaction mixture was stirred for 2 h at −60 °C and allowed to warm to rt where it was stirred for a further period of 1 h. The reaction mixture was then quenched with H_2O (5 mL), washed with aq. 1 N HCl (2 × 20 mL), extracted with ethyl acetate (3 × 50 mL). The organic layer was washed with water (50 mL) followed by brine (50 mL) and dried (Na_2SO_4). After evaporation of the solvent under vacuum, the pure ketone or aldehyde was obtained.

General procedure for the dealkylation using 2a

To a stirred suspension of NaH (from 118 mg of 60% NaH dispersion in mineral oil, 2.46 mmol) in anhydrous DMF (2 mL) at ambient temperature was added **2a** (416 mg, 2.05 mmol) in DMF (2 mL) and the mixture was stirred for 5 min. A solution of the phenolic ether or the methyl ester (0.41 mmol) in DMF (2 mL) was added and the reaction mixture was stirred at 120 °C for 3 h. Excess solvent was distilled off under low pressure. The residue was poured into aq. 1 N HCl and extracted with diethyl ether (2 × 50 mL). The ether layer was washed successively with aq. 1 N HCl and brine, and dried (Na_2SO_4). After evaporation of the solvent, the crude compound was purified either by a short silica gel column using hexane and ethyl acetate (5 : 1) as eluents or by recrystallization to afford the dealkylated products.

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17 The sulfide **3a** was dried under Dean–Stark conditions for several hours before using in the Corey–Kim oxidation.