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The fluorous Swern and Corey–Kim reactions: scope and mechanism

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Abstract—Protocols for the efficient preparation of 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluoro-8-methanesulfenyloctane and 1,1,1,2,2,3,3,4,4-nonafluoro-6-methanesulfenylhexane (fluorous dimethyl sulfide) and for their oxidation to the corresponding sulfoxides (fluorous dimethyl sulfoxide) are reported. The lower molecular weight sulfoxide, in conjunction with oxalyl chloride and Hunig's base, brings about the oxidation of diversely functionalized primary and secondary alcohols to aldehydes and ketones in excellent yield. The fluorous sulfoxide is efficiently recovered for reuse by a simple continuous fluorous extraction and hydrogen peroxide oxidation protocol. The whole process is odor-free. A deuterium-labeling experiment is used to demonstrate that the oxidations take place via the classical Swern mechanism, i.e. by intramolecular hydride abstraction from a sulfur ylid. Corey–Kim oxidations may be performed with the higher molecular weight fluorous sulfide, although recycling is not as efficient.

Environmental and economic factors have combined in recent years to force the development of cleaner, more atom-economic, efficient chemistry.[1] In this regard the advent of fluorous chemistry, first with recyclable, fluorous catalysts,[2] then with similarly recyclable fluorous reagents,[3] and most recently with protocols for the coupling of reactivity to fluorous separation,[4] has been very timely. The oxidation of alcohols is perhaps one of the most widespread, both in the research laboratory and in the production plant, but least environmentally friendly organic reactions being largely metal-based with all the associated problems of the expensive disposal of toxic waste streams. It is not surprising therefore that methodology for the oxidation of primary and secondary alcohols to aldehydes and ketones is being continually refined and improved. The focus has been largely on catalytic reactions, as typified by Ley and Griffith's tetrapropylammonium perruthenate oxidant,[5] especially the variants based on the use of oxygen as oxidants,[6] and the more recent palladium-catalyzed oxidations that also make use of air as the stoichiometric reagent.[7] Completely metal-free oxidations obviously also have much potential for environmentally friendly processes, particularly if the reagents can be readily recovered and recycled. With this in mind we turned to the examination of possible fluorous, metal-free oxidation systems. The most common metal-free systems for the oxidation of alcohols are the tempo-catalyzed systems, employing bleach as stoichiometric oxidant,[8] the Dess–Martin periodinane reagent[9] and its more user-friendly version, 2-iodoxybenzoic acid,[10,11] and the Swern reaction and its numerous variants.[12,13] Among these the Swern reaction was the most obvious choice for the development into a fluorous based system for several reasons. First, with the stoichiometric generation of dimethyl sulfide, it falls down badly on environmental grounds.[14] Second, the low molecular weight of dimethyl sulfoxide suggests that the introduction of only a single, short perfluoroalkyl chain should render it preferentially soluble in fluorous solvents. This is important in terms of economics, with the longer fluorous chains being obviously more expensive, but also in terms of practicality, especially as pertains to the need to maximize solubility. Here, we present in full the successful development and implementation of a fluorous Swern reagent, including the demonstration of mechanism.[15]

In designing the fluorous Swern reagent our primary concern was with the length of the spacer linking the fluorous chain to the sulfoxide. Reagents lacking a spacer, i.e. with the fluorous chain directly bound to the sulfoxide sulfur, were excluded from consideration as it was anticipated that they would reduce the nucleophilicity of the sulfoxide and so reduce activity. Linkers consisting of only one methylene group were tried and found wanting on the basis of the facile elimination of HF from the sulfoxide. Linkers with three or more methylene groups, while undoubtedly effective, were eliminated from consideration on the grounds that they would require a longer fluorous chain for efficient extraction. We therefore settled on a two methylene group spacer and initially selected perfluorohexyl as the fluorous chain as this would lead to a reagent with 60.2% fluorine, with 60% usually considered the lower cutoff point for efficient fluorous extraction.[16]

Keywords: oxidation; ylids; sulfoxides; fluorine and compounds.

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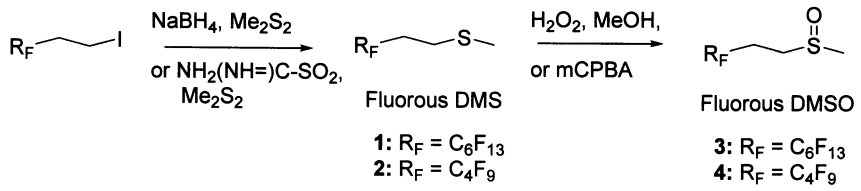


Scheme 1. Preparation of fluorous DMS and fluorous DMSO.

Reduction of dimethyl disulfide with sodium borohydride in ethanol, followed by treatment with commercial 2-perfluorohexylethyl iodide provided, after stirring overnight and standard work up, the fluorous sulfide **1** in 74% yield.[17] Alternatively, dimethyl disulfide was reduced with thiourea dioxide[18] in the presence of the fluorous alkyl iodide when the sulfide **1** was obtained in 85% yield. These direct syntheses of **1** are considerable improvements over an earlier multistep protocol, involving reaction of the iodide with sodium thiocyanate, reduction and methylation.[19] Oxidation of **1** with hydrogen peroxide in methanol[20] provided the sulfoxide **3** in high overall yield with no overoxidation to the sulfone, it having been previously determined that more forcing conditions are required for the exhaustive oxidation of **1**.[19] Oxidation with *m*CPBA was also efficacious, stopping cleanly at the sulfoxide, and resulting in a 95% isolated yield of **3**. Sulfoxide **3** was crystalline, white, and odorless but unfortunately insoluble in dichloromethane below ~ -30°C. We therefore prepared the lower homologous sulfide (**2**) and its sulfoxide (**4**) in the analogous manner in 71% overall yield from commercial perfluorobutylethyl iodide. (Scheme 1). Sulfoxide **4** is also crystalline, white, and odorless but it is soluble in dichloromethane down to -45°C. It has a fluorine content of 55.1% and is recoverable by continuous fluorous extraction, our preferred protocol,[21] and no doubt, by chromatography over fluorous silica gel.[22] The intermediate sulfide (**2**), however, is relatively volatile and in general we have converted it directly to sulfoxide **4**.

A series of oxidations were conducted in which fluorous DMSO (**4**) was activated with oxalyl chloride in dichloromethane at -30°C and subsequently treated with the substrate and then diisopropylethylamine almost as in the standard Swern oxidation. The practicality of the classical Swern protocol is therefore retained. Work-up involved brief partitioning of the reaction mixture with water, concentration of the dichloromethane solution and partitioning of the residue between toluene and FC72 (a commercial fluorous hydrocarbon) in the continuous extractor for $\approx$4 h.[21] The oxidized product (aldehyde or ketone) was then recovered from the toluene phase, while treatment of the FC72 phase with hydrogen peroxide returned the sulfoxide ready for reuse.[23] The results of these oxidations, together with the yields of recovered sulfoxide, are presented in Table 1.

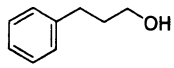
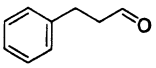
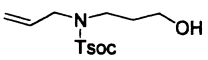
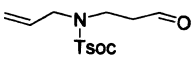
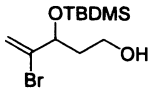
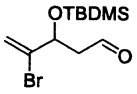
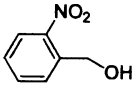
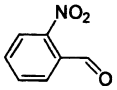
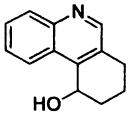
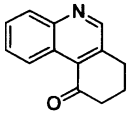
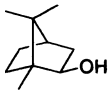
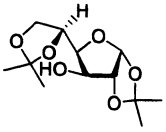
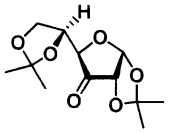
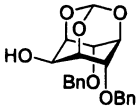
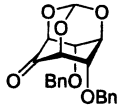
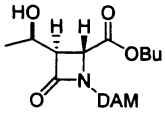
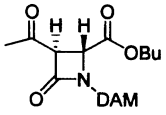
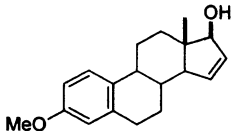
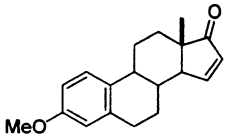
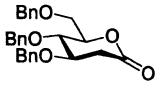
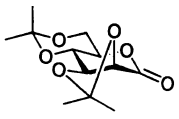
An important practical consideration in these oxidations is the exchange of dichloromethane, the reaction solvent, for toluene before the fluorous extraction. At this stage most of the sulfoxide (**4**) has been reduced to the sulfide **2**, which, itself, is very non-polar and readily recovered in the extraction protocol. However, any residual sulfoxide is not readily extracted from dichloromethane solution, presumably because of its somewhat polar nature. Replacing dichloromethane by the apolar toluene reduces the affinity of **4** for the organic phase and enables the efficient recoveries recorded in Table 1.

As is apparent from Table 1 the fluorous Swern reaction retains the mildness of conditions and applicability in the presence of a wide range of functional groups that have contributed to the popularity of the original reaction. In addition to the typical oxidations of primary and secondary alcohols we note the compatibility with Lipshutz's new triisopropylsiloxycarbonyl protecting group (entry 2),[24] the absence of β-elimination of a *tert*-butyldimethylsiloxy group (entry 3), and the oxidation of lactols to lactones (entries 11 and 12), again without β-elimination.

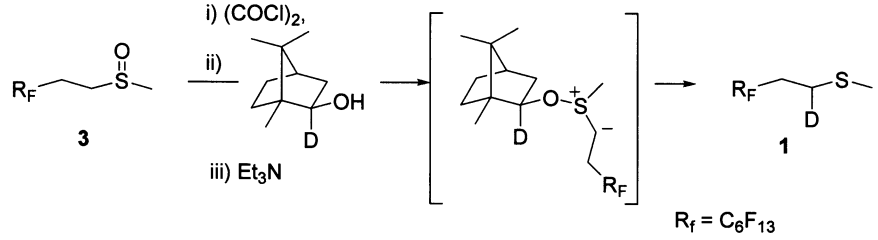
The mechanism of the fluorous Swern reaction was briefly investigated through the oxidation of monodeuterioisoborneol. Thus, camphor was reduced with lithium aluminum deuteride to give deuterioisoborneol, which was then subjected to oxidation with **3** in the normal manner. The reaction mixture was subjected to a standard aqueous work-up and the fluorous sulfide **1** was recovered by silica gel chromatography. Examination of this substance by ^{1}H NMR spectroscopy revealed a diminution in the intensity of the *S*-methylene, group as well as a change in the coupling pattern of the R_F-methylene group, consistent with the incorporation of a deuterium atom into the *S*-methylene group. This was confirmed by the ^{2}H NMR spectrum of the recovered sulfide, which exhibited a unique signal at δ 2.86. The reactions described here therefore fall into the category of true Swern oxidations and proceed via a sulfur ylid with subsequent intramolecular hydrogen transfer (Scheme 2).[25] The highly regioselective deprotonation, from the *S*-methylene rather than the *S*-methyl group, nicely illustrates the strongly electron-withdrawing nature of the fluorous chain and its effect on acidity of neighboring C–H bonds.

In addition to the Swern oxidation we have briefly investigated a fluorous version of the Corey–Kim reaction.[26] This system employs the sulfide and not the sulfoxide and hence it was possible to work with the higher homolog (**1**), taking advantage of its convenient, less volatile nature. Several examples of the successful use of this protocol are given in Table 2. However, it is important to note that in order to obtain the high recoveries of fluorous sulfide it was necessary to work with as near stoichiometric sulfide as possible. This is because any excess sulfide is oxidized by the excess NCS and is not recoverable, at least in the form of the sulfide.

Table 1. Fluorous Swern oxidations

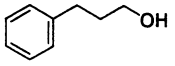
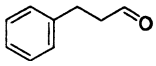
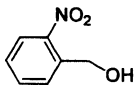
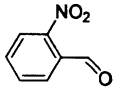
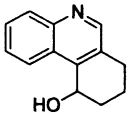
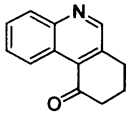
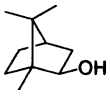
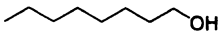
Entry	Substrate		Product	(% Yield)	% Recd **4**
1		**5**		**6** (92)	87
2		**7**		**8** (77)	84
3		**9**		**10** (91)	88
4		**11**		**12** (91)	86
5		**13**		**14** (90)	89
6		**15**		**16** (94)	90
7		**17**		**18** (83)	86
8		**20**		**21** (81)	86
9[a]		**22**		**23** (81)	84
10		**24**		**25** (80)	88
11		**26**		**27** (79)	85
12		**28**		**29** (86)	87

[a] DAM=dianisylmethyl.



Scheme 2. Incorporation of deuterium from deuterioisoborneol into sulfide **1**.

Table 2. Fluorous Corey–Kim oxidations

Entry	Substrate		Product	(% Yield)	% Recd **4**
1		**5**		**6** (83)	76
2		**11**		**12** (86)	73
3		**13**		**14** (78)	73
4		**15**		**16** (88)	72
5		**30**		**32** (88)	75

In conclusion, an efficient protocol for the preparation and application of a fluorous Swern reagent has been developed. A wide range of primary and secondary alcohols may be oxidized to the corresponding aldehydes and ketones in high yield, under completely odor free reactions. The fluorous reagent is recovered for reuse through a simple continuous fluorous extraction and reoxidation with hydrogen peroxide.

1. Experimental

1.1. General

All reagents were purchased from commercial sources and used as received, unless otherwise indicated. Tetrahydrofuran and benzene were distilled from sodium/benzophenone ketyl and methylene chloride was distilled from calcium hydride prior to use. ^{1}H, ^{2}H, ^{13}C and ^{19}F NMR spectra were recorded in deuteriochloroform solutions at 500 or 300, 77, 125 or 75, and 282 MHz, respectively. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN. All the reactions were run under a dry argon atmosphere unless and otherwise stated. With the exception of **7**, described below, oxidation substrates were either commercial or were prepared as described in the literature (**9**,[27] **13**,[28] **20**,[29] **22**,[30] **26**,[31] **28**[32]). With the exception of **8**, described below, oxidation products were identical to either commercial or literature (**6**,[33] **10**,[27] **14**,[28] **18**,[34] **21**,[29] **23**,[35] **25**,[36] **27**,[31] **29**[32]) samples.

1.2. Protocol for the preparation of fluorous sulfides and sulfoxides by borohydride reduction of dimethyl disulfide and hydrogen peroxide oxidation

$NaBH_4$ (1.4 g, 37.0 mmol) was added under Ar to a stirred solution of Me_2S_2 (3.3 g, 35.0 mmol) in EtOH (25 mL). After stirring for 30 min the reaction mixture was cooled to 0°C and a solution of perfluorobutylethyl iodide (10 g, 26.7 mmol) in anhydrous THF (15 mL) was added dropwise over 1 h. The reaction mixture was then stirred overnight at room temperature before further Me_2S_2 (1.0 g, 10.6 mmol) reduced with $NaBH_4$ (0.45 g, 11.9 mmol) in EtOH (10 mL) was added. After stirring for 6 h more, the reaction mixture was diluted with hexanes (20 mL) and washed with H_2O and brine. The hexane layer containing the sulfide **2** was diluted with MeOH (10 mL) and H_2O_2 (3.1 mL of 30%, 27 mmol) and stirred for 1 h before it was diluted with CH_2Cl_2 (25 mL), washed with H_2O, dried (Na_2SO_4) and concentrated in vacuo to give **4** (5.9 g, 19.0 mmol, 71%) as a white, crystalline solid with mp 46°C.

1.3. Alternative protocol for the formation of fluorous sulfides by thiourea sulfur dioxide reduction of dimethyl disulfide

To a mixture of perfluorohexylethyl iodide (1.0 g, 2 mmol), Me_2S_2 (0.094 g, 1 mmol), thiourea dioxide (0.11 g, 1 mmol), and cetyltrimethylammonium bromide (20 mg, 0.05 mmol) in THF (8 mL) under argon was added 6% aqueous NaOH (8 mL), followed by heating to reflux for 4–5 h. After cooling to room temperature, the organic layer was separated and the aqueous layer washed with ethyl acetate. Concentration of the extracts and flash chromatography on silica gel eluting with hexanes yielded pure fluorous sulfide **1** (0.67 g, 85%).

1.4. Alternative protocol for the oxidation of fluorous sulfides to sulfoxides with *m*CPBA

To the fluorous sulfide **1** (0.25 g, 0.6 mmol) dissolved in dichloromethane (5 mL) at −78°C was added *m*CPBA (0.14 g, 77%, 0.6 mmol) portionwise. The reaction mixture was allowed to warm to 0°C and was then stirred for a further 10 min before it was quenched by addition of sat. aqueous $NaHCO_3$. The organic layer was washed further with water and brine and the solvents evaporated to give pure crystalline **3** (0.25 g, 95%).

1.5. Fluorous sulfides and sulfoxides

1.5.1. 1,1,1,2,2,3,3,4,4,5,5,6,6-Tridecafluoro-8-methanesulfenyloctane (1). ^{1}H NMR: δ 2.76–2.73 (m, 2H); 2.47–2.36 (m, 2H); 2.18 (s, 3H); ^{13}C NMR: δ 119.9–108.7 (m), 32.3 (t), 25.1 (s), 15.9 (s); ^{19}F NMR: δ −53.8, −51.0 (d),

−50.5, −49.5, −42.0 (m), −8.5 (t). Anal. calcd for $C_9H_7F_{13}S$: C, 27.42, H, 1.79; Found: C, 27.45, H, 1.72.

1.5.2. 1,1,1,2,2,3,3,4,4-Nonafluoro-6-methanesulfenylhexane (2).[19] ^{1}H NMR: δ 2.76–2.73 (m, 2H); 2.47–2.36 (m, 2H); 2.18 (s, 3H); ^{13}C NMR: δ 117.1–108.2 (m), 32.1 (t), 25.0 (s), 15.9 (s); ^{19}F NMR: δ −53.7 (t), −52.0 (d), −42.2 (t), −8.7 (t).

1.5.3. 1,1,1,2,2,3,3,4,4,5,5,6,6-Tridecafluoro-8-methanesulfinyloctane (3). Mp 64°C; ^{1}H NMR: δ 3.04–2.98 (m, 1H); 2.92–2.86 (m, 1H); 2.72–2.61 (m, including a s at 2.68, 5H); ^{13}C NMR: δ 133.3–128.4 (m), 118.8–111.1 (m), 45.1 (s), 39.3 (s), 25.1 (t); ^{19}F NMR: δ −8.4 (d), −41.1, −49.4, −50.5, −50.8, −53.7 (d). Anal. calcd for $C_9H_7F_{13}SO$: C, 26.35, H, 1.72; Found: C, 26.29, H, 1.71.

1.5.4. 1,1,1,2,2,3,3,4,4-Nonafluoro-6-methanesulfinylhexane (4). Mp 46°C; ^{1}H NMR: δ 3.04–2.98 (m, 1H); 2.92–2.86 (m, 1H); 2.72–2.61 (m, including a s at 2.68, 5H); ^{13}C NMR: δ 133.3–128.4 (m), 118.8–108.6 (m), 45.1 (s), 39.3 (s), 25.0 (t); ^{19}F NMR: δ −8.5 (t), −41.3 (m), −51.7 (d), −53.6 (t). Anal. calcd for $C_7H_7F_9SO$: C, 27.11, H, 2.27; Found: C, 27.44, H, 2.44.

1.6. *O*-Triisopropylsilyl *N*-allyl-*N*-4-hydroxybutyl)-carbamate (7)

To a solution of 4-allylaminobutan-1-ol[37] (1.06 g, 8.27 mmol) in CH_2Cl_2 (30 mL) was added Et_3N (5.6 mL, 20.6 mmol) followed by cooling to −78°C and the bubbling of dry CO_2 for 2.5 h. TIPSOTf (2.6 mL, 9.9 mmol) was then added dropwise at −78°C and stirring continued at that temperature for 1.5 h before the solution was gradually warmed to room temperature and stirred for 2 h. The reaction mixture was then diluted with H_2O (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×70 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (3×50 mL), H_2O (2×50 mL) and brine (2×50 mL), dried (Na_2S0_4) and concentrated under reduced pressure. Purification by column chromatography on silica gel (hexanes/ethyl acetate 3:1 then gave the title compound (2.53 g, 93%) as a colorless oil. ^{1}H NMR (50°C) δ 5.83–5.73 (m, 1H), 5.16–5.09 (m, 2H), 3.86 (d, *J*=5.7 Hz, 2H), 3.63 (t, *J*=6 Hz, 2H), 3.26 (t, *J*=7.5 Hz, 2H), 1.68–1.48 (m, 4H), 1.36–1.23 (m, *J*=7.2 Hz, 3H), 1.08 (d, *J*=7.2 Hz, 18H); ^{13}C NMR δ 155.1, 134.2, 116.2, 62.5, 50.3, 49.7, 47.3, 46.7, 30.1, 29.8, 25.1, 24.5, 17.9, 17.5, 12.7, 12.2. Anal. calcd for $C_{17}H_{35}NO_3Si$: C, 61.96; H, 10.70. Found: C, 62.20; H, 10.82.

1.7. Typical protocol for oxidation with 4 and its recovery

To a well stirred solution of anhydrous CH_2Cl_2 (5 mL) under Ar at −30°C was added oxalyl chloride (0.14 mL, 1.6 mmol). A solution of sulfoxide **4** (1.0 g, 3.2 mmol) in CH_2Cl_2 (3 mL) was then added dropwise and the reaction mixture stirred for an additional 20 min. Isoborneol (0.153 g, 1.0 mmol) dissolved in CH_2Cl_2 (5 mL) was then added to this solution followed, after an additional 0.5–1 h, by $EtN(i\text{-}Pr)_2$ (0.88 mL, 5.0 mmol). The reaction mixture was then allowed to warm to room temperature and stirred for a period of 30 min before it was quenched with H_2O, washed with ammonium chloride (5 mL), extracted with CH_2Cl_2 (10 mL) and carefully concentrated under aspirator vacuum in a cold water bath. The reaction mixture was then dissolved in toluene (6 mL) and extracted continuously with FC 72 (15 mL) in a cooled continuous extractor[21] for 4 h. After decantation, concentration of the toluene layer and chromatography on silica gel yielded camphor (0.142 g, 94%). The FC-72 phase, containing a mixture of **2** and **4**, was then stirred with MeOH (3 mL) and H_2O_2 (0.23 mL of 30%, 2 mmol) for 1 h after which it was diluted with H_2O (5 mL), and extracted with CH_2Cl_2 (10 mL) in a three phase system. Concentration of the CH_2Cl_2 layer then gave recovered **4** (0.9 g, 90%).

1.7.1. *O*-Triisopropylsilyl *N*-allyl-*N*-(4-oxobutyl)carbamate (8). ^{1}H NMR δ 9.68 (t, *J*=1.3 Hz, 1H), 5.78– 5.61 (m, 1H), 5.03 (br, d, *J*=12 Hz, 2H), 3.74 (br, s, 2H), 3.13 (t, *J*=6.3 Hz, 2H), 2.37 (t, *J*=7.2 Hz, 2H), 1.75 (quintet, *J*=7.2 Hz, 2H), 1.36 (s, 9H); ^{13}C NMR δ 201.8, 155.2, 134.1, 116.6, 116.4, 116.3, 79.7, 49.8, 49.3, 45.7, 45.6, 41.1, 28.5, 23.6, 20.8. Anal. calcd for $C_{12}H_{21}NO_3$: C, 63.41; H, 9.31. Found: C, 63.16; H, 9.19.

1.8. 2-Deuterioisoborneol[38]

To a slurry of $LiAlD_4$ (0.012 g) in anhydrous ether (1 mL) was added with stirring camphor (0.1 g) in ether (2 mL) followed by heating to reflux for 3 h. After cooling to room temperature the excess hydride was decomposed by addition of moist ether then the organic layer was washed with brine, dried (Na_2SO_4) and evaporated to give a quantitative yield of deuteriated isoborneol (0.1 g). ^{2}H NMR (hexanes): δ 3.75.

1.9. Fluorous oxidation of deuterioisoborneol

The fluorous oxidation was performed with sulfoxide **3** by the standard protocol with the exception of the work up and isolation. When the oxidation was complete (TLC) the reaction was quenched with saturated aqueous NH_4Cl and the organic layer carefully concentrated. The residue was then deposited on a short silica gel column, which was eluted with hexanes. Evaporation of the eluent gave the deuteriated fluorous sulfide **1**. ^{2}H NMR (hexanes): δ 2.86.

1.10. General procedure for Corey–Kim oxidation with fluorous sulfide 1

To a solution of *N*-chlorosuccinimide (0.1 g, 0.8 mmol) in toluene (2 mL) was added **1** (0.4 g, 1 mmol) at 0°C resulting in the immediate formation of a white cloudy precipitate. The reaction mixture was cooled to −25°C and a solution of octanol (0.07 g, 0.5 mmol) in toluene (2 mL) was added. After stirring at −25°C for 2 h a solution of Et_3N (0.08 g, 0.8 mmol) was added. The cold bath was removed after 5 min and the reaction mixture washed with sat. aqueous NH_4Cl, then water. The organic layer was extracted continuously with FC 72 (15 mL) in a cooled continuous extractor for a period of 4 h. Concentration of the toluene layer and chromatography on silica gel (eluent: EtOAc/hexanes 3:1) yielded octanal (0.06 g, 88%). The FC-72 layer was carefully concentrated under

aspirator vacuum to give the recovered fluorous sulfide **1** (0.3 g, 75%).

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