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## Accepted Article

**Title:** A Simple, Mild and General Oxidation of Alcohols to Aldehydes or Ketones by SO<sub>2</sub>F<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub> Using DMSO as Solvent and Oxidant

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# A Simple, Mild and General Oxidation of Alcohols to Aldehydes or Ketones by $\text{SO}_2\text{F}_2/\text{K}_2\text{CO}_3$ Using DMSO as Solvent and Oxidant


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**Abstract.** A practical, general and mild oxidation of primary and secondary alcohols to carbonyl compounds proceeds in yields of up to 99% using  $\text{SO}_2\text{F}_2$  as electrophile in DMSO as both the oxidant and the solvent at ambient temperature. No moisture- and oxygen-free conditions are required. Stoichiometric amount of inexpensive  $\text{K}_2\text{CO}_3$ , which generates easy to separate by-products, is used as the base. Thus, 5-gram scale runs proceeded in nearly quantitative yields by a simple filtration as the work-up. The use of a polar solvent such as DMSO, which usually promotes competing Pummerer rearrangement, is also noteworthy. This protocol is compatible with a variety of common N-, O-, and S-functional groups on (hetero)arene, alkene and alkyne substrates (68 examples). The protocol was applied (99% yield) to a formal synthesis of the important cholesterol-lowering drug Rosuvastatin.

**Keywords:** oxidation; alcohols; carbonyl compounds; sulfuryl fluoride; sulfoxide

Aldehydes and ketones are key intermediates in the synthesis of a large variety of versatile pharmaceuticals, fine chemicals, vitamins, fragrances, materials and other chemical transformations.<sup>[1]</sup> Therefore, the development of methods for selective oxidation of alcohols to aldehydes or ketones while avoiding undesirable over-oxidation to carboxylic acids, esters or other by-products is of great importance in both academic research and industrial chemical production.<sup>[2]</sup> Although a large variety of transition-metal-catalyzed approaches (using Pd, Ru, Fe, Cu, Pt, Au, Ir, Rh, etc.) are available for selective oxidation of alcohols to aldehydes or ketones, the use of conventional non-catalytic oxidation processes is still the most predominating strategy for oxidation of alcohols to aldehydes (ketones) in both laboratories and industry.<sup>[3]</sup> Numerous non-catalytic oxidants,

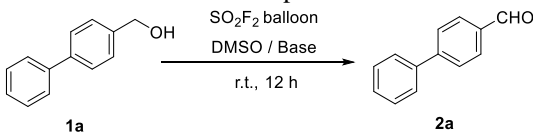
such as the chromium or manganese-based species (e.g.,  $\text{CrO}_3$ , pyridinium chloro- and dichromate,  $\text{MnO}_2$ ,  $\text{KMnO}_4$ ),<sup>[4]</sup> hypervalent iodine reagents,<sup>[5]</sup> and activated sulfoxides,<sup>[6]</sup> particularly dimethyl sulfoxide (DMSO), have all been successfully employed for non-catalytic selective oxidation of alcohols. Among them, the latter has been established as one of the most powerful and useful oxidants for alcohol oxidation without the use of environmentally-harmful heavy metals. In the past several decades, great efforts have been spent to develop suitable electrophilic reagents as activators for DMSO such as carbodiimides (Pfitzner–Moffatt oxidation),<sup>[7]</sup> trifluoroacetic or acetic anhydrides or oxalyl chloride (Swern Oxidation),<sup>[6g,8]</sup>  $\text{SO}_3\cdot\text{Py}$  (Parikh–Doering oxidation),<sup>[9]</sup>  $\text{P}_2\text{O}_5$  or  $\text{SO}_3$ ,<sup>[10]</sup> phosgene,<sup>[11]</sup> bis(trichloro-methyl)carbonate<sup>[12]</sup> and cyanuric chloride,<sup>[13]</sup> among others. Unfortunately, almost all of the above suffer from common disadvantages:<sup>[14]</sup> (1) low temperatures to prevent undesired Pummerer rearrangement as well as generation  $\text{H}_2\text{C}=\text{S}(+)\text{-CH}_3$  species, which is highly reactive towards alcohols in a non-productive fashion; (2) narrow range of compatible non-polar solvents, typically  $\text{CH}_2\text{Cl}_2$ , to minimize the formation of methylthioalkyl ethers; (3) challenging handling of the highly moisture-sensitive, irritating and toxic electrophilic activators; (4) large excess of organic base, typically  $\text{Et}_3\text{N}$ , which produces large amounts of organic waste and necessitates tedious work-up and purification. A "perfect" electrophilic activator capable of negating at least most of these drawbacks for laboratorial and industrial chemistry would be highly desirable.

Sulfuryl fluoride ( $\text{SO}_2\text{F}_2$ ), a colorless, odorless, inexpensive (about 1\$/kg),<sup>[15a]</sup> and relatively inert gas (stable up to 400 °C when dry) has recently attracted significant attention as an electrophile to react with phenols under mild basic conditions.<sup>[15]</sup> Herein, we

report, to the best of our knowledge, the first example of using  $\text{SO}_2\text{F}_2$  as a "perfect" activator for selective oxidation of alcohols to carbonyl compounds in DMSO as both solvent and oxidant at room temperature only using 1 equiv. of an inexpensive and easy to remove inorganic base.

To achieve the above, several main challenges needed to be addressed. The use of the non-toxic DMSO not only as oxidant but also as solvent would maximize the product yield. However, polar solvents have rarely been successful in this class of oxidations.<sup>[8, 14]</sup> Next, relatively high temperatures (ambient and above) are required for reactions with  $\text{SO}_2\text{F}_2$  (for instance, pure  $\text{SO}_2\text{F}_2$  is unreactive up to 400 °C)<sup>[15b]</sup> but can lead to undesirable Pummerer rearrangement. Finally, inorganic bases are highly advantageous due to low cost, ease of separation and product purification, and formation of relatively benign byproducts but have generally not been successful when used alone in Swern type of oxidations.

**Table 1.** Reaction conditions optimization<sup>a, b</sup>

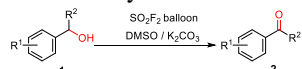


Entry	Base (equiv.)	Conversion (1a, %) <sup>b</sup>	Yield (2a, %) <sup>b</sup>
1 <sup>c</sup>	$\text{Et}_3\text{N}$ (2.0)	50	49
2	$\text{Et}_3\text{N}$ (2.0)	100	95
3	none	2	0
4 <sup>d</sup>	$\text{Et}_3\text{N}$ (2.0)	49	48
5	$\text{K}_2\text{CO}_3$ (2.0/1.0)	100/99	99/96
6	$\text{Cs}_2\text{CO}_3$ (2.0)	100	89
7	$\text{Na}_2\text{CO}_3$ (2.0)	42	41
8	$\text{KF}$ (2.0/1.0)	100/52	98/52
9	$\text{KOAc}$ (2.0/1.0)	89/84	85/83
10	$\text{K}_2\text{CO}_3$ (1.2)	100	99

<sup>a)</sup> Reaction conditions: A 25-mL round-bottomed flask was charged with 4-Biphenylmethanol (**1a**, 0.2 mmol), base, DMSO (1.5 mL) and  $\text{SO}_2\text{F}_2$  (*Caution! Toxic by inhalation. Use only in well-ventilated fume hoods.*) was introduced by bubbling into the solution *via* a balloon. The mixture was stirred at RT over 12 h. <sup>b)</sup> The yields and conversion were determined by HPLC using **2a** or **1a** as the external standards ( $t_{2a} = 4.5$  min,  $\lambda_{\text{max}} = 289$  nm;  $t_{1a} = 3.4$  min,  $\lambda_{\text{max}} = 289$  nm, respectively; methanol/water = 80 : 20 (v / v)). <sup>c)</sup> DMSO (3.0 mmol, 15 eq.) in  $\text{CH}_2\text{Cl}_2$  (1.5 mL). <sup>d)</sup>  $\text{Et}_3\text{N}$  was added after 12 h, and the reaction mixture was stirred for additional 12 h.

The feasibility of the  $\text{SO}_2\text{F}_2/\text{DMSO}$  alcohol oxidation was evaluated (Table 1; see SI for full details) using 4-biphenylmethanol (**1a**). To our delight, 50% of the starting material **1a** was consumed upon exposure to excess of gaseous  $\text{SO}_2\text{F}_2$  and DMSO (3.0 equiv.) at room temperature in  $\text{CH}_2\text{Cl}_2$  using  $\text{Et}_3\text{N}$  (2.0 equiv.) as the base, giving the desired 4-biphenyl aldehyde **2a** in 49% yield over 12 h (Table 1, entry 1). With DMSO as the sole reaction solvent, the conversion of **1a** and the yield of **2a** increased to 100% and 95%, respectively (Table 1, entry 2). Without  $\text{Et}_3\text{N}$ , alcohol **1a** remained intact; delayed addition of  $\text{Et}_3\text{N}$  caused sluggish conversion (49% after 12 hours); the yield of **2a** was 48% (Table 1, entries 3 and 4). Among inorganic bases,  $\text{K}_2\text{CO}_3$  performed excellently, giving **2a** in 99% yield at 2.0 and 1.2 (optimal) equiv., and 96% at 1.0 equiv. loading (Table 1, entries 5 and 10, respectively).  $\text{Cs}_2\text{CO}_3$  was slightly, and  $\text{Na}_2\text{CO}_3$  significantly less effective (Table 1, entries 7 and 8). Interestingly,  $\text{KF}$  also proved highly effective, giving **2a** in 98% at 2.0 equiv. but only 52% at 1.0 equiv. loading (Table 1, entry 8). The weaker  $\text{KOAc}$  was also effective (~85% yield of **2a** at both 2.0 and 1.0 equiv. loading; Table 1, entry 9).

**Table 2.** Oxidation of Benzylic Alcohols.<sup>a</sup>



2a, R <sup>2</sup> = Ph, 97%	2f, R <sup>2</sup> = Cl, 98%	2k, R <sup>2</sup> = CF <sub>3</sub> , 90%	2p, R <sup>1</sup> = OMe, 94%	2t, R <sup>2</sup> = OMe, 56%
2b, R <sup>2</sup> = OMe, 92%	2g, R <sup>2</sup> = Br, 90%	2l, R <sup>2</sup> = COOMe, 99%	2q, R <sup>1</sup> = Br, 99%	2u, R <sup>2</sup> = Br, 91%
2c, R <sup>2</sup> = OBn, 98%	2h, R <sup>2</sup> = I, 95%	2m, R <sup>2</sup> = SMe, 97%	2r, R <sup>1</sup> = CN, 92%	2v, R <sup>2</sup> = I, 36%
2d, R <sup>2</sup> = H, 99%	2i, R <sup>2</sup> = CN, 94%	2n, R <sup>2</sup> = SO <sub>2</sub> Me, 94%	2s, R <sup>1</sup> = CF <sub>3</sub> , 92%	2w, R <sup>2</sup> = NO <sub>2</sub> , 67%
2e, R <sup>2</sup> = F, 92%	2j, R <sup>2</sup> = NO <sub>2</sub> , 88%	2o, R <sup>2</sup> = NHAc, 94%		

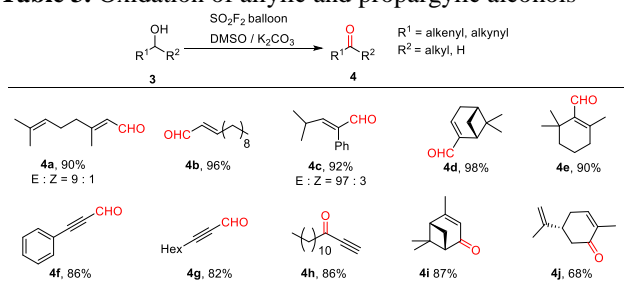
2x, 98%	2y, 99%	2z, 97%	2aa, 92%	2ab, 96%	2ac, 91%	2ad, 98%
2ae, 92%	2af, 53%	2ag, 33%	2ah, 92%	2ai, 90%	2aj, 46%	2ak, 98%
2al, 70%	2am, 97%	2an, 75%	2ao, 97%	2ap, 99%	2aq, 94% <sup>b</sup>	
2ar, 63%	2as, 84%	2at, 70%	2au, 63%	2av, 99%	2aw, 62%	

<sup>a)</sup> Reaction conditions: A 50-mL round-bottomed flask was charged with the required alcohol (**1a-aw**, 0.2 mmol),  $\text{K}_2\text{CO}_3$  (331 mg, 2.4 mmol) and DMSO (15 mL) and  $\text{SO}_2\text{F}_2$  was introduced by bubbling into the solution *via* a balloon. The mixture was stirred at RT over 12 h. <sup>b)</sup>  $\text{K}_2\text{CO}_3$  (662 mg, 4.8 mmol), DMSO (20 mL) were used.

Under optimized conditions (Table 1, entry 10), a large number of functionalized benzylic alcohols were transformed to the corresponding benzylic aldehydes (**2a-aw**) in good to excellent yield (Table 2). *m*- And/or *p*-substituted benzylic alcohols (Table 2) gave higher benzaldehyde yields (e.g. **2b**, **2j**, **2g**, and **2p**), whereas the *o*-substituents moderately depressed product yields (e.g. **2t**, **2v**, and **2w**). The compatibility with thioether (**2m**; 97%) is noteworthy. Heteroarylmethanols derived from furan (**1ao**), benzothiophene (**1an**), pyridine (**1ad-al**, **1aw**), indole

(**1am**) and 2,1,3-benzooxadiazole (**1ap**) were all oxidized smoothly to their corresponding aldehydes (yields up to 99%; >90% in most cases). However, pyridylmethanols possessing *m*-electron-withdrawing groups (**1af**, **1ag**) afforded **2af**, **2ag** in significantly lower yields (53% and 33% respectively). 1,4-Phenylenedimethanol (**1aq**) was also oxidized to terephthal-aldehyde (**2aq**) in 94% isolated yield. Secondary benzylic alcohols were also liable to oxidation giving the corresponding ketones, albeit with lower yields on average (e.g., **2a**, 97% and **2ar**, 63%).

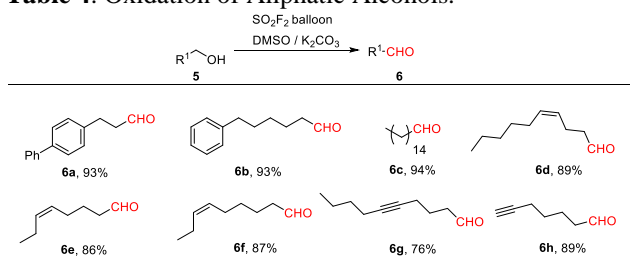
**Table 3.** Oxidation of allylic and propargylic alcohols <sup>a</sup>



<sup>a</sup>) Reaction conditions: same as Table 3 employing alcohols **3a-j**.

Next, good to excellent yields were also attained for oxidation of primary and secondary allylic and propargylic alcohols to  $\alpha$ ,  $\beta$ -unsaturated carbonyl compounds (Table 3). (*E*)-allylic alcohol **3a** afforded the corresponding aldehyde **4a** in 90% yield with a slight loss of stereochemical integrity (*E*/*Z* = 9:1). On the other hand, **3b** provided the  $\alpha$ ,  $\beta$ -enal **4b** in 96% yield with 100% of retention of (*E*)-configuration. Similarly, **3c** was converted to **4c** in 92% yield maintaining the initial *E*/*Z* ratio of 97:3. More complex allylic primary terpene alcohols such as (1*R*)-(-)-myrtenal (**3d**), and  $\beta$ -cyclogeraniol (**3e**) were oxidized to the corresponding aldehydes **4d** and **4e** in 98% and 90% yields. The analogous secondary alcohols **3i** and **3j** gave **4i** and **4j** in somewhat lower yields (87% and 68%, respectively). Propargylic alcohols (**3f**, **g**, **h**) were also smoothly oxidized to  $\alpha$ ,  $\beta$ -ynals **4f**, **g** and  $\alpha$ ,  $\beta$ -ynone **4h** in 82-86% yields.

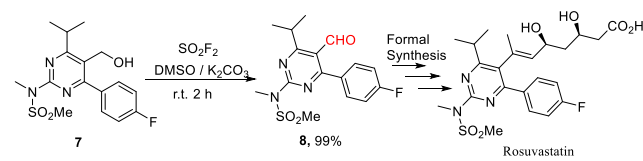
**Table 4.** Oxidation of Aliphatic Alcohols.<sup>a</sup>



<sup>a</sup>) Reaction conditions: same as Table 3 employing alcohols **5a-h**.

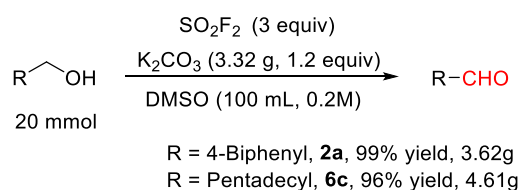
Aliphatic alcohols (**5a-c**) were also smoothly oxidized (Table 4) to aldehydes **6a**, **6b** and **6c** in 93%, 93%, and 94% yields, respectively. Unsaturated long-chain aliphatic alcohols (**5d-5h**) afford their

corresponding aldehydes (**6d-6h**) in good to excellent yields without affecting the unsaturated functionality.



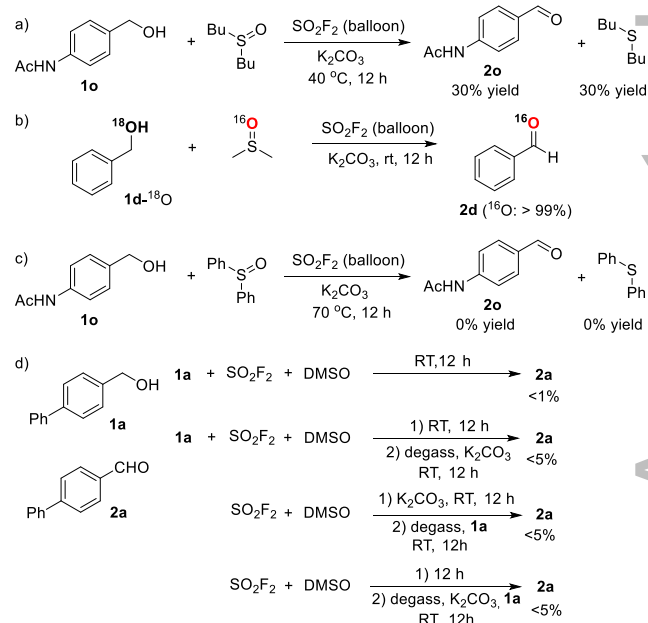
**Scheme 1.** Application of  $\text{SO}_2\text{F}_2/\text{DMSO}$  oxidation to formal synthesis of Rosuvastatin.

The preparation of the pyrimidinyl aldehyde **8**, a key precursor en route to Rosuvastatin (Crestor<sup>TM</sup>, a blockbuster HMG-CoA reductase inhibitor)<sup>[16]</sup> from the highly functionalized alcohol **7** was accomplished smoothly to provide aldehyde **8** in 99% yield without chromatography (Scheme 1). This formal synthesis<sup>[17]</sup> of the drug demonstrates well the utility the  $\text{SO}_2\text{F}_2/\text{DMSO}$  oxidation in target-oriented synthesis of complex molecules.

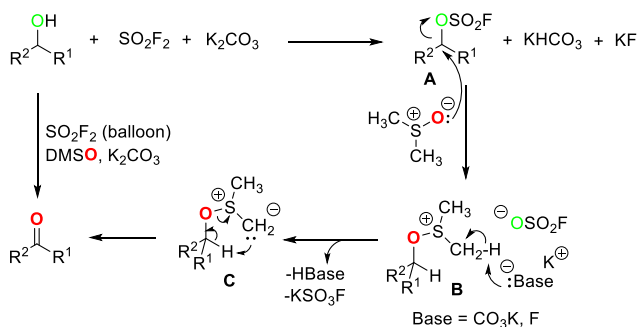


**Scheme 2** Gram-Scale Runs.

Oxidations of 4-biphenylmethanol (**1a**) and 1-hexadecanol (**5c**) on 20-mmol scale (~5 g) gave **2a** and **6c** in 99% and 96% yields, respectively, indicating good scalability for the method (Scheme 2).



**Scheme 3.** a) The use of *n*- $\text{Bu}_2\text{SO}$  in the place of DMSO produces equal amounts of aldehyde and the reduced product *n*- $\text{Bu}_2\text{S}$ . b) Oxidation of an <sup>18</sup>O labeled substrate. c) The use of  $\text{Ph}_2\text{SO}$  in the place of DMSO obtained no  $\text{Ph}_2\text{S}$  or desired aldehyde **2a**. d) Control experiments for the role of the base.



**Figure 1.** The proposed base-regeneration mechanism for the SO<sub>2</sub>F<sub>2</sub>/DMSO oxidation.

Conducting the oxidation of **1o** in dibutylsulfoxide gave equimolar ratio of oxidation product **2o** (30 % yield) and isolated dibutyl sulfide (Scheme 3a). The oxidation of <sup>18</sup>O-labeled **1d** gave **2d** that was  $\geq 99\%$  <sup>16</sup>O-labeled (Scheme 3b). Both results support that the sulfoxide was the source of the carbonyl oxygen in the product. The use of diphenylsulfoxide did not proceed the oxidation indicating the generation of sulfonium ylides as essential intermediate (Scheme 3c). Mixing of the reactants without K<sub>2</sub>CO<sub>3</sub> (similar to Table 1 entry 3); mixing of the reactants then adding K<sub>2</sub>CO<sub>3</sub> after removal of SO<sub>2</sub>F<sub>2</sub> by degassing; pre-mixing SO<sub>2</sub>F<sub>2</sub>, K<sub>2</sub>CO<sub>3</sub> and DMSO over 12 h, then removing SO<sub>2</sub>F<sub>2</sub> and adding **1a**; or pre-mixing SO<sub>2</sub>F<sub>2</sub> and DMSO over 12 h, then removing SO<sub>2</sub>F<sub>2</sub>, and adding **1a** and K<sub>2</sub>CO<sub>3</sub> all resulted in negligible yield of **2a** (Scheme 3d).

A mechanism consistent with the results of these experiments was thus proposed (Figure 1).<sup>[18]</sup> Formation of a fluorosulfate ester of the alcohol to be oxidized and SO<sub>2</sub>F<sub>2</sub> in the presence of the base is followed by an S<sub>N</sub>2-displacement (consistent with the observed higher yields for primary alcohols and lack of elimination/Wagner-Meerwein shift by-products detected) by DMSO acting as the nucleophile. This generates the same cationic intermediate as produced in Swern-type oxidation. The reaction ends with base-generated sulfur ylide followed by intramolecular deprotonation-elimination of Me<sub>2</sub>S as generally accepted. The mechanism thus proposed in principle requires 2 equiv. of base one is consumed during fluorosulfate formation, the other during ylide generation. An important effect arising from the use of the "perfect electrophile" SO<sub>2</sub>F<sub>2</sub> is the generation of 1 equiv. fluoride after the consumption of the alcohol. Use of KF by itself leads to high aldehyde yields, suggesting that fluoride is capable (pK<sub>a</sub> of HF in DMSO is 15 ± 2)<sup>[19]</sup> of forming sulfur ylide in the context of Swern-type oxidation - the first time this has been observed (to the best of our knowledge). The high yields obtained with only 1 equiv. of K<sub>2</sub>CO<sub>3</sub> KOAc (Table 1) thus can be rationalized by generation of KF in the first stage, which then is used during the second stage of the reaction. We attribute this to the significant thermodynamic gain associated with irreversible conversion of the alcohol to fluorosulfate by the "click reagent" SO<sub>2</sub>F<sub>2</sub> and the formation of KSO<sub>3</sub>F in contrast with the reversible carbonate formation in Das' protocol.<sup>[20]</sup>

In summary, a simple, mild, versatile and scalable (up to ~5 g) protocol for oxidation of alcohols to carbonyl compounds with SO<sub>2</sub>F<sub>2</sub>/K<sub>2</sub>CO<sub>3</sub> in DMSO as both solvent and oxidant was developed. A broad range of alcohols (benzylic, allylic, propargylic, and aliphatic) carrying a large variety of functional groups were selectively oxidized at room temperature without the requirement of strictly anhydrous or oxygen-free conditions as well as without deleterious methylthioalkyl ether formation or Pummerer rearrangement. Mechanistically, the reaction involves a base-promoted conversion of the alcohol by the relatively inert inorganic gas SO<sub>2</sub>F<sub>2</sub> (stable up to 400 °C when dry), to a fluorosulfate ester and fluoride. Nucleophilic displacement by DMSO produces an intermediate identical to the one formed by the typical Swern-type oxidation. Base-promoted elimination of Me<sub>2</sub>S and KSO<sub>3</sub>F completes the reaction. Importantly, we observed for a first time that fluoride was an effective promoter for sulfur ylide generation in activated DMSO oxidations. The fluoride base (re)generation explains the high yields attainable with only ~1 equiv. of base; the inexpensive and non-toxic K<sub>2</sub>CO<sub>3</sub> emerged as the best choice. Such an inorganic base is more environmentally benign due to the formation of easy to separate non-toxic by-products compared to the typical organic bases used for activated DMSO oxidations as demonstrated by the preparation of an advanced intermediate towards the cholesterol-lowering drug Rosuvastatin in 99% yield and high purity by simple work-up.

## Experimental Section

### General procedures for oxidation reactions

#### General procedure A

To an oven-dried reaction flask charged with a stir bar (50 mL), alcohol (2 mmol), K<sub>2</sub>CO<sub>3</sub> (331 mg, 2.4 mmol) and DMSO (15 mL, 0.13 M) were added, the flask was then covered with a plastic stopper, before SO<sub>2</sub>F<sub>2</sub> gas (sulfuryl fluoride) was introduced *via* a needle from a balloon of the gas (degassed with SO<sub>2</sub>F<sub>2</sub> for 10~30 seconds). The reaction mixture was vigorously stirred at room temperature for 12 h. When the alcohol had been consumed (Monitoring by TLC), the reaction mixture was poured into water (100 mL), extracted with diethyl ether (3 × 25 mL). The combined organic layers were then washed with water (3 × 25 mL) and dried over anhydrous sodium sulfate. Evaporation of solvent under reduced pressure gave the title compounds.

#### General procedure B

When the oxidation was completed, the reaction mixture was poured into water (100 mL), and extracted with EtOAc (3 × 25 mL). The combined organic layers were then washed with water (3 × 25 mL) and dried over anhydrous sodium sulfate. The crude product was purified by silica gel chromatography by gradient elution with 5–20% EtOAc / Petroleum ether to give pure product.

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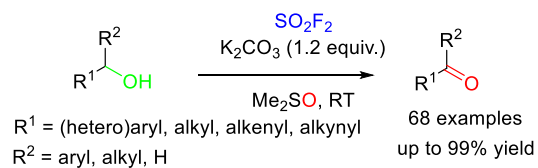
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## COMMUNICATION

A Simple, Mild and General Oxidation of Alcohols to Aldehydes or Ketones by  $\text{SO}_2\text{F}_2/\text{K}_2\text{CO}_3$  Using DMSO as Solvent and Oxidant

*Adv. Synth. Catal.* **Year**, *Volume*, Page – Page

Gao-Feng Zha,<sup>a,†</sup> Wan-Yin Fang,<sup>a,†</sup> Jing Leng,<sup>a</sup> and Hua-Li Qin<sup>a\*</sup>



- ✓ DMSO as oxidant and solvent
- ✓ Highly atom-economic
- ✓ Conducted at room temperature
- ✓ Moisture and air tolerable
- ✓ Wide scope and excellent functional groups tolerance
- ✓ Up to 5-g scale using only easy to separate reagents
- ✓ Formal synthesis of the drug Rosuvastatin