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Oxidation of Sulfides with a Silica-Supported Peracid in Supercritical Carbon Dioxide under Flow Conditions: Tuning Chemoselectivity with Pressure

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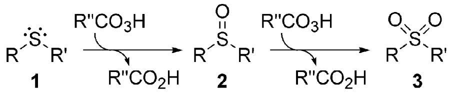
Supercritical carbon dioxide is a convenient medium for performing the selective oxidation of sulfides **1** to either sulfoxides **2** or sulfones **3** with [2-percarboxyethyl]-functionalized silica (**4**) under flow conditions. The chemoselectivity of the reaction, which results from the different diffusion rates of sulfide and sulfoxide over the reagent bed, can be controlled by adjusting the pressure and the hydration of the silica surface as both the solvating power of the mobile phase and the surface activity of the stationary phase determine the migration rates of sulfide **1** and sulfoxide **2** over the supported peroxide. The results elucidate the impact of surface phenomena on the course of chemical reactions carried out under flow conditions.

Introduction

Supercritical carbon dioxide[1] (*sc*CO_2) is a convenient medium for performing heterogeneous chemical reactions[2] because its low surface tension, low viscosity, and high diffusivity[1] allow the substrate solution to reach the reactive sites on the active surface much better than conventional liquid solvents. These properties of *sc*CO_2, along with its readily accessible critical conditions (T_c = 31.0 °C; P_c = 73.8 bar), benign character, low cost, and the existence of a technology platform for the application of *sc*CO_2 in large-scale continuous-flow processes have extended the potential of this medium for application as a green solvent for chemical reactions.

The density and transport properties of *sc*CO_2 depend on the pressure, which allows for continuous adjustment of the solvating ability of the medium without changing the nature of the solute–solvent interactions.[1] This unique tunable character of supercritical fluids has proven most useful for solid nucleation, extractive and chromatographic processes in *sc*CO_2 with applications in the food and pharmaceutical industries.[1] Heterogeneous reactions in which solid matrices are used as either catalysts or insoluble supports for reagents or catalysts should also be sensitive to pressure in *sc*CO_2, as changes in the solvating ability of the solvent modify the interactions of the active surface with catalysts, reagents, products or transition states, which can alter the reaction course.[3] In order to explore this possibility, we studied the oxidation of sulfides with a silica-supported peracid in *sc*CO_2 under flow conditions. In this reaction, the peracid performs two consecutive oxygen-transfer steps to the substrate [Equation (1)], the first being faster than the second. The distinct interactions of the competing sulfide **1** and sulfoxide **2** with the silica surface under different reaction conditions could overcome this kinetic preference and thereby change the reaction chemoselectivity.



(1)

We report herein that the oxidation of sulfides **1** with hydrated [2-percarboxyethyl]-functionalized silica (**4**) in *sc*CO_2 under flow conditions can be tuned to selectively yield sulfoxides **2** or sulfones **3** by adjusting the pressure. The results are interpreted in terms of the distinct transport of the competing sulfide **1** and sulfoxide **2** over the silica surface under the specific reaction conditions, which depends on the solvating power of *sc*CO_2 and the adsorbing ability of the silica surface. The reaction chemoselectivity observed in conventional solvents under flow conditions differs from that obtained in *sc*CO_2, suggesting that surface diffusion plays a major role in the migration of the substrates along the reagent bed. The results show the importance of surface phenomena in reactions carried out under flow conditions over supported reagents or catalysts, and illustrate the application of the tunable character of *sc*CO_2 to control the reaction course.

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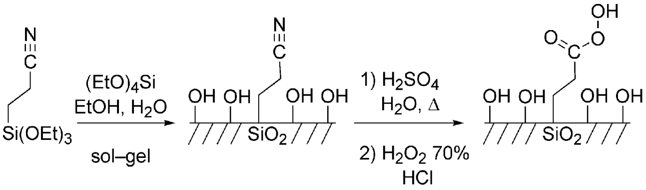
Results and Discussion

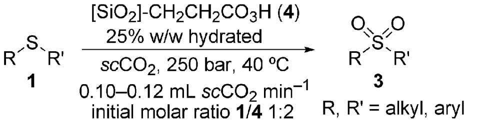
Silica-supported peracid **4** was prepared[4] by acid hydrolysis of [2-cyanoethyl]-functionalized silica, obtained by a standard sol–gel method, followed by treatment of the resulting [2-carboxyethyl]-functionalized silica with 70% hydrogen peroxide in acidic medium (Scheme 1). Lyophilization of the solid reagent yielded a 22–26% w/w hydrated material. Analysis of the hybrid materials by conventional ^1H NMR apectroscopy according to a reported procedure[5] showed a load of 2.5–3.5 mmol of organic ligands per gram. Iodometric titration of [2-percarboxyethyl]-functionalized silica (**4**) showed loads of 0.8–1.7 mmol of peracid/g. The silica-supported peracid **4** was stored at –20 °C for weeks without a noticeable loss of peroxidic titer. The reagent can be recycled[2a,4] by reaction of the hybrid material with aqueous hydrogen peroxide under acidic conditions.



Scheme 1. Synthesis of the supported peracid (**4**).[4]

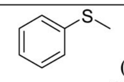
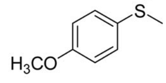
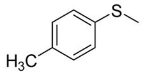
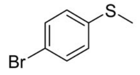
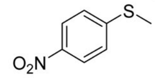
Oxidations in *sc*CO_2

The first series of experiments was carried out with a 1:2 initial molar ratio of sulfide **1**/peracid **4** in order to verify the reactivity of the supported peracid towards sulfides **1** and sulfoxides **2**. Oxidations were carried out by flowing *sc*CO_2 (0.10–0.12 mL *sc*CO_2 min^{-1}) at 250 bar and 40 °C for 3 h through a reservoir containing the substrate **1** (0.5 mmol), and then through a column packed with 25% w/w hydrated reagent **4** [Equation (2)]. The system was depressurized through a micrometric valve and the reaction products were collected in a trap cooled to –78 °C. The residue obtained was dissolved in dichloromethane and analyzed by gas chromatography. Products were characterized by gas chromatography/mass spectrometry, ^1H and ^{13}C NMR spectroscopy. Mass balances were correct in all cases, indicating that the reaction products were not retained on the silica surface under these conditions. The results are shown in Table 1 (Method A). The silica-supported reagent recovered from the column had a white color and a loose appearance in all cases. Iodometric titration of the consumed reagent showed a loss of peroxidic titer corresponding to the oxygen-transfer performed to the substrate. The control experiments carried out with a 2:1 initial molar ratio of methyl phenyl sulfide (**1a**)/peracid **4** led to the complete consumption of the peracid, showing that all the peroxidic ligands on the silica surface are accessible to the substrate.



(2)

Table 1. Oxidation of sulfides **1** with the silica-supported peracid **4** in *sc*CO_2 under flow conditions.

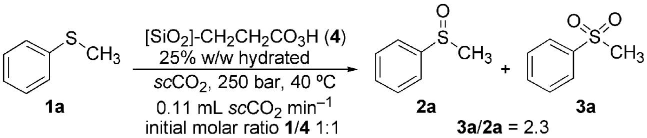
	Method A[a]		Method B[b]	
	Conv. (%)	**3/2**	Conv. (%)	**3/2**
 (**1a**)	95	29.8	73	0.27
 (**1b**)	>99	270	98	0.13
 (**1c**)	99	13.6	98	0.46
 (**1d**)	87	11.1	89	0.17
 (**1e**)	95	4.2	90	0.02
Ph_2S (**1f**)	85	4.4	99	0.11
(n-$C_4H_9)_2S$ (**1g**)	93	5.8	85	0.15

[a] Reactions at 250 bar, 40 °C and flow rate 0.10–0.12 mL *sc*CO_2 min^{-1}; load of peroxide: 1 mmol of peracid g^{-1}; hydration of **4**: 25% w/w; molar ratio of **1**/**4** was 1:2. [b] Reactions in *sc*CO_2 at 100 bar, with anhydrous **4**, and a 1:1 molar ratio of **1**/**4**; products were eluted with a solution of methanol in *sc*CO_2.

The results we had previously obtained[2a,2k] in the oxidation of organic substrates with supported peracids in *sc*CO_2 under flow conditions showed that an excess of oxidant was required to achieve the complete conversion of the substrate. This fact was attributed to the shorter contact time of the substrate solution with the supported reagent in the flow reactions compared to the batch reactions. The results in Table 1 reveal that the reactions of both sulfides **1** and sulfoxides **2** with the supported peracid **4** are fast enough to obtain the corresponding sulfone **3** as the main product in all cases. The oxygen transfer to the substrates **1**, though generally high, was in no case quantitative. The substrate conversion and the sulfone **3**/sulfoxide **2** ratio obtained for the different sulfides **1a**–**g** indicate that the reaction efficiency depends on the substrate structure (Table 1, Method A). Thus, sulfides **1** with electron-withdrawing substituents showed lower conversions and lower sulfone/sulfoxide ratios than those substrates with electron-releasing substituents (Table 1). In addition, sterically demanding substituents on sulfide **1** led to less efficient and less selective reactions. For instance, the substrate conversion and the sulfone **3**/sulfoxide **2** ratios were 95% and 29.8 for methyl phenyl sulfide (**1a**), 93% and 5.8 for dibutyl sulfide (**1g**) and 85% and 4.4 for diphenyl sulfide (**1f**), respectively.

These results are in agreement with the reaction mechanism proposed for the oxygenation of sulfides **1** and sulfoxides **2** with organic peracids in solution.[6,7]

The oxidation of methyl phenyl sulfide (**1a**) with a stoichiometric amount of 25% w/w hydrated oxidant **4** in *sc*CO_2 was carried out at 250 bar and 40 °C under flow conditions (0.11 mL *sc*CO_2 min^{-1}), according to the same procedure described above [Equation (3)]. Analysis of the organic material recovered in the cold trap showed a substrate conversion of 49% and a **3a**/**2a** ratio of 2.3. A thorough washing of the solid reagent with dichloromethane did not allow the recovery of additional amounts of organic material.



(3)

This result does not follow the reactivity pattern of sulfides **1** and sulfoxides **2** towards organic peracids in solution,[6,7] in which sulfoxides **2** are the major products in the reaction of sulfides **1** with stoichiometric amounts of peracid. Considering that the oxidation of methyl phenyl sulfide (**1a**) to methyl phenyl sulfone (**3a**) with the organic peracid **4** implies two successive oxygen transfer steps [Equation (1)] and that methyl phenyl sulfoxide (**2a**) is less reactive than sulfide **1a** towards **4**,[6,7] the formation of **3a** as the main product strongly suggests that the reaction conditions determine a competitive advantage for sulfoxide **2a** to react with peracid **4** when compared to sulfide **1a**.

The main features of the oxidation of methyl phenyl sulfide (**1a**) under continuous flow over a supported peracid **4** are: (i) substrate and products migrate along the reagent bed driven by the flow vector, (ii) the migration rates for sulfide **1** and sulfoxide **2** are determined by their interactions with the silica surface, which are stronger for the latter given its higher basicity and polarity, (iii) the intermediate sulfoxide **2** competes with sulfide **1** for peracid **4**, and (iv) peracid **4** is consumed in the oxidation steps. In a simplified view, the migration of the substrates along the reagent bed would involve a series of successive desorption/convection transport/adsorption steps.[8] Thus, if the intermediate sulfoxide **2** does not significantly adsorb on the silica surface, the concentration of sulfide **1** in the stream of *sc*CO_2 entering the reagent bed would rapidly be converted to the corresponding sulfoxide **2** as the solution advances over the supported peracid **4**. The flow of *sc*CO_2 would transport the sulfoxide **2** toward a region of the reagent bed with a higher load of unreacted peroxidic ligands, where it would be oxidized in the absence of competing sulfide **1**. Under these conditions, sulfone **3** would be the main product of the reaction. Conversely, if the sulfoxide **2**, formed by oxygen transfer from the peracid to the sulfide **1**, remains hydrogen-bonded to the acidic silica surface, then sulfide **1**, which is less retained because of its weaker Lewis-base character, would be transported preferentially towards the unreacted peroxide. As a result, sulfoxide **2** would be the main product of the reaction. Thus, the efficiency of the mobile phase in transporting sulfoxide **2** along the reactive stationary phase would determine the chemoselectivity of the reaction. As *sc*CO_2 is a tunable solvent, which permits increasing the number of solute–solvent interactions by raising the pressure,[1] the reaction chemoselectivity should be pressure-dependent.

The nature of the silica surface contributes also to establishing the magnitude of the adsorption equilibrium constant.[8] Our previous results in the oxidation of organic substrates with supported peroxides[2a,2k] have shown that coordination of water molecules to the acidic sites on the active surface diminishes its acidic strength, and thereby its ability to adsorb polar substrates. The ^1H NMR analysis of the 25% hydrated silica-supported peracid **4** (ca. 14 mmol of water per gram of hybrid material) showed a load of 2.5 mmol of organic ligands and 5.6 mmol of silanol groups per gram of material.[5] The hydration layer in this case consists of ca. 2 molecules of water for each acidic position (silanol, carboxylic acid or peracid). Further hydration of this solid material provides less strongly bonded water molecules and diminishes accordingly the ability of the silica surface to adsorb polar substrates.

Since the solvating ability of *sc*CO_2 and the adsorbing ability of the silica surface are tunable by changing the pressure or by hydration, respectively, we can predict that higher pressures and higher hydration of the supported reagent **4** would favor the formation of sulfone **3** in these reactions.

In order to verify the influence of these parameters on the chemoselectivity of the reaction, we examined the effect of pressure on the oxidation of methyl phenyl sulfide (**1a**) in *sc*CO_2 under flow conditions with differently hydrated supported peracids **4**. The oxidation of methyl phenyl sulfide (**1a**) was carried out by flowing *sc*CO_2 (0.12 mL *sc*CO_2 min^{-1}) at 40 °C and at pressures ranging from 100 to 300 bar, for 3 h through a reservoir containing the substrate (0.5 mmol), and then through a column packed with the silica-supported peracid **4** (initial molar ratio sulfide/peracid 1:1). The reactions were carried out with anhydrous, 25% and 50% w/w hydrated supported peracid **4**. The anhydrous peracid **4** was prepared by drying the solid reagent under vacuum at room temperature until it reached a constant weight. Hydration was performed by adding the desired amount of water to this reagent and then allowing the mixture to equilibrate at 4 °C for 12 h. The products were collected by depressurization in a trap cooled to –80 °C and by moisturizing the solid reagent recovered from the column and then washing thoroughly with dichloromethane. Substrate conversions and product distributions were determined by GC analysis of the combined residues. Mass balances were satisfactory in all the cases.

The results, which are shown in Figure 1, fit nicely with the model described above. Thus, the anhydrous silica-supported peracid **4** strongly retains sulfoxide **2a** over the whole range of pressures used and, consequently, the ratio **3a/2a** is consistently low along the series. In this case, the main reaction product was sulfoxide **2a**, which was completely desorbed from the silica surface by flowing a solution of methanol in *sc*CO_2 over the supported reagent once the reaction had been completed. The series of reactions with the 25% w/w hydrated reagent **4** showed that an increased pressure of up to 250 bar reversed the selectivity of the reaction. A further increase of the pressure to 300 bar enhanced the overoxidation of the sulfide up to **3a/2a** = 2.5. This trend became more evident with the 50% w/w hydrated silica-supported peracid **4** (ca. 7 water molecules for each acidic ligand). In this case, the selectivity **3a/2a** of the reaction could be tuned from 0.34 to 12.6 by increasing the pressure from 100 bar to 300 bar. In these experiments, the reaction products were collected exclusively from the cold trap.

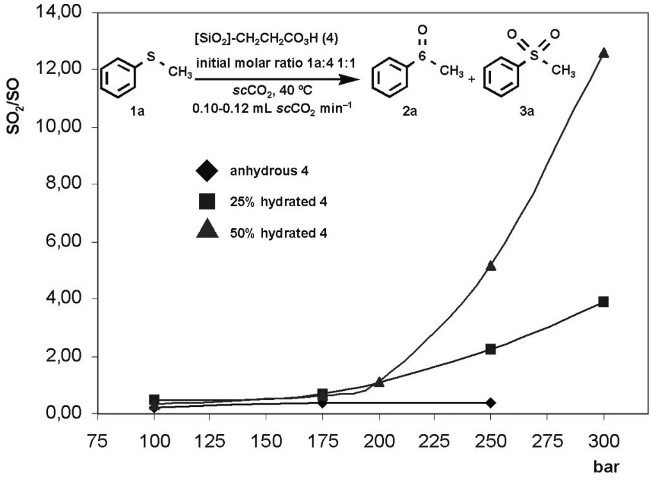
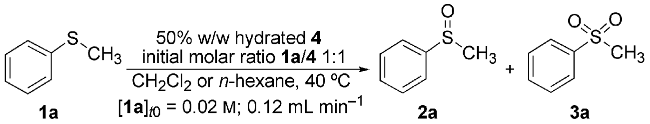


Figure 1. Oxidation of methyl phenyl sulfide (**1a**) in *sc*CO_2 under flow conditions (0.12 mL *sc*CO_2 min^{-1}) at different pressures with anhydrous (diamonds), 25% w/w (squares) and 50% w/w (triangles) supported peracid **4**.

According to these results, the selective oxidation of sulfides **1** to the corresponding sulfoxides **3** was performed by flowing *sc*CO_2 (0.12–0.10 mL *sc*CO_2 min^{-1}) at 100 bar and at 40 °C for 3 h through a reservoir containing the substrate **1** (0.5 mmol), and then through a column packed with 1 equiv. of the anhydrous silica-supported peracid **4**. Sulfoxides **3** were recovered in the cold trap by flowing a solution of methanol in *sc*CO_2 at 250 bar over the reagent bed for 1 h (Table 1, Method B). The process was successful even for the most reactive sulfides.

Oxidations in Conventional Solvents

Oxidation of methyl phenyl sulfide (**1a**) with 50% w/w hydrated silica-supported peracid **4** in conventional solvents provides further information on the solvent properties of *sc*CO_2 and the physicochemical processes taking place on the silica surface. The experiments under flow conditions were carried out at 40 °C by eluting a 0.02 M solution of **1a** in dichloromethane or hexane through a column packed with reagent **4** in the same solvent at 0.12 mL min^{-1}. The solid reagent in the column was thoroughly washed with the solvent, and the solution was analyzed by gas chromatography. The results are shown in Scheme 2.



	Conv. (%)	3a/2a
CH_2Cl_2	81	0.26
n-hexane	70	0.67

Scheme 2. Oxidation of sulfide **1a** with 50% w/w hydrated silica-supported peracid **4** in conventional solvents under flow conditions.

The reactions in the liquid solvents under flow conditions gave methyl phenyl sulfoxide (**2a**) as the main reaction product (Scheme 2), in clear contrast to the results obtained in *sc*CO_2 at high pressures (Figure 1). These experimental results cannot be interpreted in terms of a simplified transport mechanism exclusively involving successive desorption/convection transport/adsorption steps. In fact, this model predicts that increasing the solvating ability of the solvent will diminish the adsorption equilibrium constant for sulfoxide **2a**, thus facilitating its convection transport towards the unreacted peracids on the stationary phase and increasing sulfone **3a** formation Accordingly, sulfone **3a** formation should be more efficient not only in liquid solvents than in *sc*CO_2, but also in dichloromethane than in *n*-hexane. However, the reverse is observed experimentally, indicating the involvement of an alternative transport mechanism for sulfoxide **2a** that is favored in the less-solvating media.

The results can be rationalized by considering that the migration of sulfoxide **2a** along the reagent bed also takes place by surface diffusion,[8,9] in which the adsorbate migrates by successive shifts from its initial adsorption site to an adjacent acidic ligand without leaving the surface, promoted by thermal activation or collisions with the solvent. Hydration of the silica surface facilitates surface diffusion as the water molecules lower the acidity of the surface ligands and provide a continuous protic layer that interconnects the acidic sites on the silica surface.[9] Under these conditions, the activation energy for surface diffusion is lower than for desorption,[8,9] because the adsorbed substrate remains hydrogen-bonded to the silica surface in the former, while it breaks the hydrogen-bonding interaction as it is transferred into the solution in the latter. Accordingly, the migration of the adsorbed sulfoxide **2a** along the silica surface would take place by successive adsorption/surface diffusion/desorption/convection transport steps. Adsorption/desorption equilibrium and rate constants determine both the efficiency of the long-range convection transport and the residence time of the substrate on the silica surface, while the surface diffusion coefficient determines the distance covered by the substrate during its stay on the silica surface. In competitive reactions with silica-supported reagents or catalysts, the substrate that better adsorbs and diffuses on the reagent surface will have a competitive advantage in colliding with the reagent or catalyst immobilized on the silica surface.

The chemoselectivity observed in the oxidation of sulfide **1a** with 50% w/w hydrated silica-supported peracid **4** in different solvents and under flow conditions results from the balance of different surface phenomena under the specific reaction conditions. The adsorption equilibrium constant is larger for sulfoxide **2a** than for sulfide **1a**, and the residence time at the silica surface is longer for the former. As the solvating ability of the solvent diminishes, both parameters increase. Consequently, less-solvating media enhance the competitive advantage of sulfoxide **2a** over sulfide **1a** to react with the silica-supported peroxide **4**. This is the pattern observed experimentally (Figure 1, Scheme 2). For the anhydrous silica-supported peracid **4**, the lack of a continuous protic network on the silica surface minimizes the surface diffusion coefficient for sulfoxide **2a**, because the stronger acid character of the active surface and the distance between the ligands make the required hydrogen-bond interchanges difficult.

Surface diffusion under flow conditions is directional as adsorbed sulfoxide **2a** diffuses along the reagent bed driven by collisions with the solvent. Accordingly, the effect of pressure on the reaction chemoselectivity observed in the oxidation of sulfide **1a** with the 50% w/w hydrated supported peracid **4** in *sc*CO_2 reveals that the efficiency of the surface transport increases as the solvent density increases. The experimental data also show that surface diffusion is more efficient in *sc*CO_2 at high pressures than it is in conventional solvents. This result can be attributed to the high diffusivity of *sc*CO_2, which minimizes solvent stagnation in the less accessible regions of the silica surface and improves the transport of the substrates by both convection and surface diffusion along the reagent bed.

The kinetic effect of *sc*CO_2 on the relative reaction rates of sulfide and sulfoxide with organic peracids has not been determined in this study. The higher reactivity of sulfides **1** over sulfoxides **2** toward organic peracids observed in solution arises[6b,7] from the differences in the solvation of substrates and transition states. This kinetic effect is stronger for polar solvents than for apolar solvents, although the trend is maintained even in CCl_4 or *n*-hexane.[6b] By considering that the quadrupole moment of CO_2[10] permits Lewis acid–Lewis base interactions with polar functional groups and imparts “polar” attributes to *sc*CO_2 as a solvent,[11] and that reactions take place in the polar protic environment of the silica surface, the kinetic effect of *sc*CO_2 on the oxidation of sulfide **1a** with the silica-supported peracid **4** is expected to play a minor role in the preferential formation of methyl phenyl sulfone (**3a**) under our reaction conditions.

Conclusions

The oxidation of sulfides **1** with hydrated [2-percarboxyethyl]-functionalized silica (**4**) in *sc*CO_2 under flow conditions can be tuned to give either sulfoxides **2** or sulfones **3** by adjusting the pressure. The reaction chemoselectiviy, which results from the different diffusion rates of the competing sulfide **1** and sulfoxide **2** over the reagent bed, depends on the surface activity of the supported reagent and the solvating power of *sc*CO_2. The results indicate the importance of surface phenomena in reactions carried out under flow conditions over supported reagents or catalysts, and the potential of the tunable transport properties of *sc*CO_2 for the control of the selectivity in these cases. This heterogeneous procedure improves the product isolation step with regard to the conventional homogeneous reaction conditions, as it involves a simple depressurization and avoids the wastes associated with the carboxylic acid neutralization. The silica-supported peracid **4** can be recycled by treatment with hydrogen peroxide under acidic conditions.

Experimental Section

CAUTION! The experiments described in this paper involve the use of relatively high pressures and require equipment with the appropriate pressure rating.

General: [2-Percarboxyethyl]-functionalized silica (**4**) was prepared as described elsewhere.[2a,4] Dichloromethane was purified according to described procedures.[12] The glassware used in the reactions with 70% hydrogen peroxide was carefully cleaned and washed before use with a solution of EDTA in ultrapure water (0.25 $g\,L^{-1}$) to remove metal traces. The peroxidic content of the supported reagent was determined by standard iodometric titration. Hydration of the silica-supported peracid **4** was performed by adding to a weighed sample of anhydrous functionalized silica the desired amount of ultrapure water, and allowing the mixture to equilibrate at 4 °C in a tightly closed vial for 12 h. The high-pressure equipment consisted of a 250-mL AISI 316 stainless-steel jacketed autoclave, a diaphragm pump (Orlita MHS 30/8) with a maximum theoretical flow of 8.44 L/h of liquid CO_2, and a set of high-pressure valves, pressure and temperature probes and safety rupture-discs suitably placed to control the flow of CO_2 along the system.

Oxidation of Sulfides (1) with [2-Percarboxyethyl]-Functionalized Silica (4) in *sc*CO_2. Method A. General Procedure: Methyl phenyl sulfide (**1a**) (0.12 mL, 1 mmol) was placed in a U-shaped stainless-steel tubing, which was connected through suitable fittings to a stainless steel 8 mm ID column packed with 25% w/w hydrated silica-supported peracid **4** (2 g, 1.0 $mmol\,g^{-1}$, 2 equiv.). Two filters placed at either end of the column prevented displacement of the solid reagent throughout the experiment. The outlet of the column was connected to a high-pressure micrometric valve which was connected to a trap cooled with a dry-ice bath through a 1/8 inch Teflon tubing. The pressure in the trap was equilibrated with a flow of nitrogen. The inlet of the substrate reservoir was connected with a high-pressure valve to a 250 mL autoclave set at 40 °C. The autoclave was closed, charged with CO_2 and pressurized to 250 bar. Then both the substrate reservoir and the column were placed into a water bath heated to 40 °C, and the system was allowed to pressurize by carefully opening the inlet valve. The stroke volume of the pump and the aperture of the high-pressure micrometric outlet valve were regulated to achieve steady continuous flow conditions at 250 bar. The CO_2 flow at the outlet of the system was monitored with a bubble flow meter. The system was left to operate for 3 h. The inlet valve was then closed, and the system was allowed to depressurize. The trap was warmed to room temperature, and the colorless residue was dissolved in deuterated chloroform and analyzed with the aid of GC, GC–MS, ^1H, and ^{13}C NMR techniques. The solid reagent recovered from the column was washed four times with 15 mL of dichloromethane in a round-bottomed flask with magnetic stirring. The filtered solution was analyzed by means of GC and then concentrated under vacuum at 0 °C.

Oxidation of Sulfides (1) with [2-Percarboxyethyl]-Functionalized Silica (4) in *sc*CO_2. Method B. General Procedure: Methyl phenyl sulfide (**1a**) (0.12 mL, 1 mmol) was placed in a 0.2 mL loop of a Rheodyne valve, which was connected through suitable fittings to a stainless steel 8 mm ID column packed with anhydrous silica-supported peracid **4** (0.83 g, 1.2 mmol g^{-1}, 1 equiv.). Two filters placed at either end of the column prevented displacement of the solid reagent throughout the experiment. The outlet of the column was connected to a high-pressure micrometric valve, which was connected to a trap cooled with a dry-ice bath through a 1/8 inch Teflon tubing. The pressure in the trap was equilibrated with a flow of nitrogen. The inlet of the Rheodyne valve was connected with a high-pressure valve to a 250 mL autoclave set at 40 °C. The autoclave was closed, charged with CO_2 and pressurized to 100 bar. Both the Rheodyne loop and the column were then placed into a water bath heated to 40 °C, and the system was allowed to pressurize by carefully opening the inlet valve. The stroke volume of the pump and the aperture of the high-pressure micrometric outlet valve were regulated to achieve steady continuous flow conditions at 100 bar. The CO_2 flow at the outlet of the system was monitored with a bubble flow meter. The substrate was injected, and the system was left to operate for 3 h. Afterwards, the pressure was raised to 250 bar, and the CO_2 flow was fixed again to 0.10–0.12 mL of *sc*CO_2 min^{-1}. Six portions of 0.2 mL of methanol were successively injected through the Rheodyne valve at 10 min intervals. The system was then allowed to depressurize. The trap was warmed to room temperature, and the solution was concentrated under vacuum. The colorless residue was dissolved in deuterated chloroform and analyzed with the aid of GC, GC–MS, ^1H, and ^{13}C NMR techniques. The solid reagent recovered from the column was washed four times with 15 mL of dichloromethane in a round-bottomed flask with magnetic stirring. The filtered solution was analyzed by means of GC and then concentrated under vacuum at 0 °C.

Supporting Information (see footnote on the first page of this article): GC–MS, ^1H and ^{13}C NMR spectra of the reaction mixtures.

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