Clean Oxidation

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Cleaner Continuous Photo-Oxidation Using Singlet Oxygen in Supercritical Carbon Dioxide**

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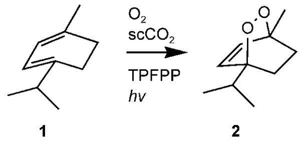
Singlet oxygen, $^1O_2$, is widely used in contemporary organic synthesis.[1] $^1O_2$, is also an efficient electron acceptor leading[2] to the formation of superoxide radical ion $O_2^{\cdot -}$. Both $^1O_2$ and $O_2^{\cdot -}$ have been implicated in the biosynthesis of some natural products and in biochemical processes and harnessing singlet oxygen to aid in the construction of the complex molecular motifs found in natural products is a subject of current research.[3] Two of the most convenient and "clean" methods for introducing oxygen into hydrocarbon substrates involve reactions of $^1O_2$ either with alkenes, leading to allylic alcohols, or with 1,3-dienes leading to endoperoxides. Both of these synthetic transformations have been used as pivotal steps in a number of natural-product syntheses[4] and also in the synthesis of perfume ingredients.[5] Furthermore, the addition of O_2 is 100% atom efficient, unlike more conventional oxidations where half of the oxygen atoms are usually wasted, often in the form of H_2O or CO_2, although, some of this atom efficiency may be lost in subsequent steps.

The most common method used to generate $^1O_2$ in the laboratory, is by photoexcitation of molecular oxygen, generally in the presence of a photosensitizer.[6] $^1O_2$ can also be generated thermally with sodium hypochlorite and hydrogen peroxide[7] or from Ph_3PO_3[8] or oxone.[9] The widespread application of photochemistry on a large scale in industry has not yet proved feasible.[10] There are severe scale-up limitations with photochemical reactors and new reactor designs are required to overcome the decrease in photochemical reaction efficiency as the concentration of reagents is increased to the high-concentration conditions compatible with industrial-scale processes. The higher reactivity and relatively short lifetime of $^1O_2$ gives rise to a serious technical problem; namely a solvent is required which is non-flammable and which is relatively slow in relaxing the $^1O_2$ back to its triplet ground state. Traditionally CCl_4 has been the solvent of choice but it is no longer acceptable from an environmental standpoint. Other solvents, such as iso-propanol, have been used[11,12] but there are problems of potential flammability.

Experiments have demonstrated that it is possible to generate $^1O_2$ with a reasonably long lifetime (5.1 ms at 14.7 MPa and 314 K) in supercritical carbon dioxide ($scCO_2$).[13–16] Recently we demonstrated[17] how $^1O_2$ can be used in homogeneous reactions by using a perfluorinated photosensitizer which is soluble in $scCO_2$. In addition, both the non-flammability of CO_2 and high solubility of O_2 in the compressed-gas solvent[18,19] give potential advantages. The complete miscibility of O_2 with CO_2 allows the system to be safely kept below the explosion limits, significantly reducing the risks of the reaction. $scCO_2$ also has much lower viscosity and higher diffusivity than traditional solvents thus overcoming mass-transfer limitations that are found in traditional multiphasic systems.[20]

Using the batch synthesis of ascaridole (**2**) from α-terpinene (**1**) as an example, we monitored the kinetics using in situ FTIR which demonstrated[17] that $scCO_2$ can give improved performance over CCl_4, with the reactions being at least two-times faster in $scCO_2$ (Scheme 1). However, in the interests of safety, our high-pressure experiment[17] was carried out on a very small scale with no more than 30 μL of product being isolated in any experiment.



Scheme 1. Photo-oxidation of α-terpinene to ascaridole; TPFPP = 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin.

Clearly any useful process in $scCO_2$ will require scaling up and scaling up-high pressure systems presents several technical challenges. The first is to increase the volume of the reaction vessel without increasing the optical pathlength unduly and thereby avoiding "inner filter" effects which would prevent the bulk of the fluid from reacting photochemically. More generally, the cost of high-pressure vessels themselves becomes prohibitive as they are made larger. Such considerations have dictated that scale-up of supercritical processes usually involves a switch from batch to continuous processing.[21]

There have been a number of reports of using continuous photochemical reactors for $^1O_2$ both in conventional glassware and microreactors.[22–24] Although relatively efficient in terms of conversion, these reactors have been rather low in their overall productivity (which, for example, is only in the $\mathrm{mmol\,L^{-1}\,min^{-1}}$ range) and require relatively high electrical power consumption for the lamps.

Our group has pioneered the use of small-scale continuous photochemical reactors for the synthesis of organome-

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tallic compounds in $scCO_2$ and other supercritical solvents.[18,25,26] We have also developed larger scale continuous reactors[27–29] for heterogeneous catalysis in $scCO_2$, culminating in the construction of a full-scale 1000 tons per annum chemical plant.[21] Herein we describe a continuous reactor for the photochemical reactions of $^1O_2$ which considerably improves efficiency compared to reactors for conventional solvents. Our reactor has two innovative features: 1) a very simple tubular sapphire reactor which provides a relatively long irradiation zone and 2) illumination by high-power visible-light-emitting diodes (LED), such as used for automobile headlights, the small size of which permit efficient illumination of the cell without any additional optics. Herein, we describe our continuous-flow reactor, illustrate its operation with a successful 3000-times scale-up of our synthesis of **2**, apply the reactor to the photo-oxidation of citronellol (**3**), the first stage in the synthesis of Rose Oxide (**8**), and show that the combination of our reactor and the LEDs can provide a substantial improvement in efficiency compared to conventional solvents.

Safety warning*: the reactions described involve high pressures and should only be carried out in an apparatus with the appropriate pressure rating and with due regard to the potentially explosive reaction between* O_2 *and organic compounds.*

The essential component in our approach to scale up is the photolysis cell, shown in Figure 1, which is based on a miniature sapphire view cell which was successfully used[30,31] for the supercritical synthesis for the series of new gas solvates of C_{60} including $C_{60}(CO_2)_x$, $C_{60}(C_2H_4)_x$, and $C_{60}(C_2H_6)_x$.

The cell consists of a sapphire tube sealed into a stainless steel holder by O-ring seals which can slide to accommodate differential thermal expansion. The advantage of this arrangement is that a relatively narrow sapphire tube can be used with a large proportion of its length available for irradiation and not obscured by the mounts. Our design differs from more conventional sapphire tubular view cells[32] which normally have much greater diameter with thicker walls which necessitates long optical paths and hence the possibility of inner filter effects. The internal diameter of our tube is 7.8 mm, the wall thickness is 1.2 mm, and the total volume is 5.7 mL of which the irradiated volume is 4.1 mL. In its present configuration the cell is unheated because a sufficient temperature rise is caused by the LEDs. We use eight composite 1000 lumen white LEDs (OSTAR; Part Code: LE UW E3B-PZQZ-4C8F), each of which is composed of a cluster of six individual diodes; the LEDs are mounted as two arrays of four LEDs on commercial aluminum heat sinks. On the scale of our apparatus, the LEDs are effectively point light sources with a divergence of 130°. This arrangement means that when the LEDs are mounted approximately 0.5 cm from the sapphire cell that the majority of the light passes through the cell. With all eight LEDs running at full power, the internal temperature of the sapphire cell can rise to as high 70 °C; therefore modest cooling is achieved by blowing air over the cell using a commercial ventilation fan (Bionaire B299 fanheater).

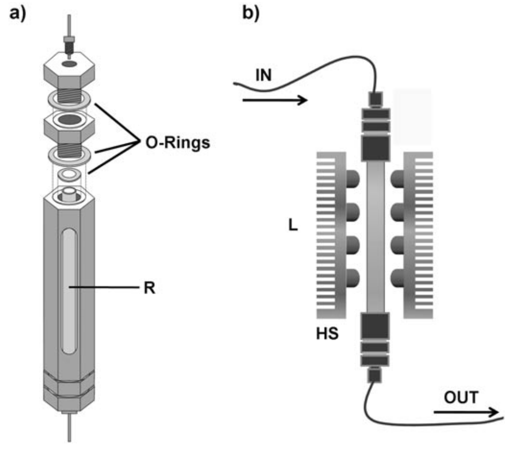


Figure 1. a) Schematic diagram of the sapphire tube reactor (R), shown in its reactor housing. The sapphire tube is held in place by a pair of EPDM rubber O rings, and a 1/8 inch Autoclave Engineer fitting allows connection to the apparatus. b) Diagrammatic view of the LED irradiation of the sapphire tube reactor with two LED arrays (L), each containing four 1000 lumen LEDs positioned approximately 5 mm from the sapphire tube. Each array is mounted on an aluminum heat sink (HS), cooled by two 5 cm diameter fans (not shown).

It is important to stress that the generation of $^1O_2$ only requires visible light. The efficiency of current LEDs is much higher in the visible region than in the UV. Therefore it is possible to achieve high "wall plug" efficiency with visible LEDs; indeed the efficiency could be increased further by using narrowband LEDs with a wavelength tuned to the specific photosensitizer being used. However, we have chosen to use broadband visible LEDs so that we can change photosensitizer without modifying the photolysis source.

The sapphire cell is mounted in the continuous-flow system (Figure 2). In a typical experiment, liquid CO_2 was pumped at 2.0 mL min^{-1} (pump head at −10 °C, 48 bar), the organic reactant containing the photosensitizer was pumped at 0.2 mL min^{-1}, and O_2 was dosed in (see Figure 1) at a rate of two molar equivalents of O_2 to organic reactant.

We have proved the principle and operation of our reactor by performing the oxidation of **1** to **2** (Scheme 1), the reaction that we have previously carried out under batch conditions in a cell of total volume of 2 cm^3. The photosensitizer, 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (TPFPP), is soluble in both **1** and **2** and all three components are soluble in the $scCO_2/O_2$ mixture.[17] Quantitative conversion could be achieved in a single pass through our reactor with flow rates of substrate up to 0.2 mL min^{-1}. The reactor operated with unchanged efficiency over 8 h without any noticeable fouling of the sapphire tube. This feature is particularly important as fouling of windows is often a significant problem in many photochemical reactions.[33] This 8 h run yielded 96 mL of **2** with less than 0.5 % **1** as shown by ^{1}H NMR spectroscopy. This result represents a × 3000 scale-up of our original batch reaction.

As a more stringent test of our flow reactor, we have studied the photo-oxidation of citronellol (**3**), a key step in the synthesis of Rose Oxide (**8**), a fragrance of commercial value (Scheme 2).

This reaction presents a number of challenges to our approach namely 1) the sensitizer TPFPP is insufficiently

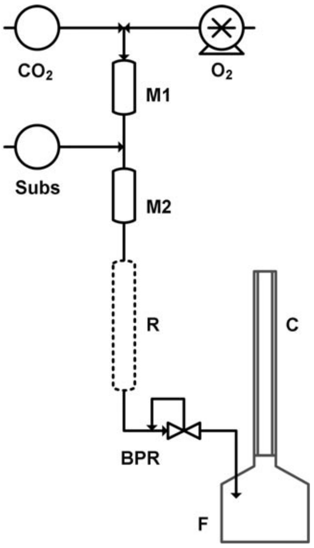


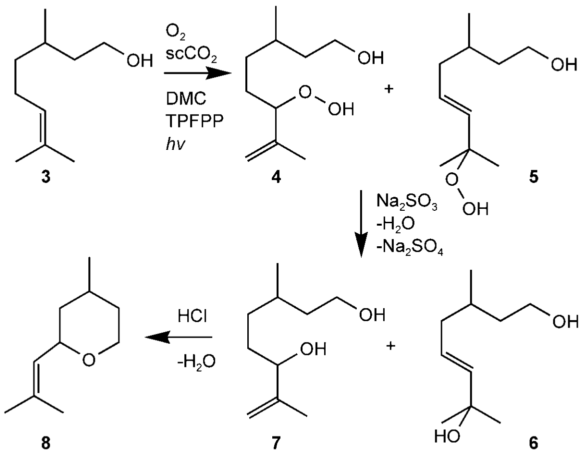
Figure 2. The photochemical flow system. CO_2 is delivered from a chilled Jasco PU-1580-CO2 pump. O_2 is added at a measured rate by a Rheodyne dosage unit. The organic substrate and photosensitizer solution are pumped using a Jasco PU-980 HPLC pump. The CO_2 and O_2 are passed through a mixer (M1; 5 cm 1/4 inch SS316 tubes at 50 °C) and then mixed with the substrate stream (subs), which passes through a second mixer (M2). The mixed stream then passes into the sapphire tube reactor (R), and then flows out continuously through a Jasco BP-1580-81 back-pressure regulator (BPR). The material is then collected in a glassware flask (F), with attached condenser (C).

soluble in pure **3** to be used in the same way as with **1** and 2) the hydroperoxide products, **4** and **5** are virtually immiscible with $scCO_2$. The solubility problem with TPFPP was overcome by addition of a 1:1 *v*:*v* of dimethyl carbonate (DMC), to **3**. DMC is a relatively highly oxidized compound which we have used for a range of reactions in $scCO_2$,[34] in addition DMC does not react with $^1O_2$.

The first stage of our investigation was phase-behavior studies both of the continuous reaction mixture and the products. The volume of our phase analyzer is relatively large and therefore using O_2 represents a safety hazard;[35] N_2 has very similar properties to O_2 in terms of phase behavior at room temperature and is an acceptable substitute for O_2. Our phase measurements on $\mathbf{3}+\mathrm{DMC}+\mathrm{TPFPP}+scCO_2+N_2$, demonstrate that a single-phase mixture can be obtained under the reaction conditions (Figure 3). Similar experiments with the hydroperoxide products confirm that they are indeed insoluble possibly because of increased hydrogen bonding but our continuous reactor can cope with biphasic reaction mixtures provided it is operated in a downflow configuration.

The next stage was to carry out a batch reaction to establish the reaction kinetics using a single white LED as the photolysis source. In the absence of suitable IR bands we monitored the reaction by the pressure drop as the O_2 was consumed. Figure 4 shows that the pressure falls linearly with time indicating a zero-order reaction, as might be expected if the rate determining step is the absorption of light by TPFPP. The reaction of $^1O_2$ with **3**, is relatively unselective and gives an almost equimolar mixture of **4** + **5** which can be converted into **8** in the subsequent work-up.

We repeated the reaction using our continuous-flow reactor. The single-pass conversion of **3** at 0.1 $\mathrm{mL\,min^{-1}}$ (1:1 *v*:*v* DMC:**3**), 1.0 $\mathrm{mL\,min^{-1}}$ of CO_2, 2 equivalents of O_2 at 180 bar was again 100 % with 52 % selectivity to **4** and 48 % selectivity to **5**. The reaction was performed for approximately 4 h converting 12 mL of **3**. Since **4** and **5** are considerably less stable than ascaridole, **2**, which is itself potentially explosive, we carried out the majority of our experiments by collecting the products directly into an aqueous solution of Na_2SO_3. This approach ensured that **4** and **5** were converted into **6** and **7** as soon as they were delivered from the reaction system. The co-solvent DMC is completely soluble in water and so it did not present a problem. In one experiment, we tried running the reactor in upflow but the immiscibility of **4** and **5** with $scCO_2$ led to the accumulation of liquid in the sapphire tube; therefore all subsequent experiments were performed in downflow. It is important to stress that any cloudiness caused by incipient



Scheme 2. Reaction pathway for the conversion of **3** into **8**. Photo-oxidation of **3**, subsequent reduction to diol products **6** and **7**, and then acidification to yield Rose Oxide (**8**). DMC = dimethyl carbonate.

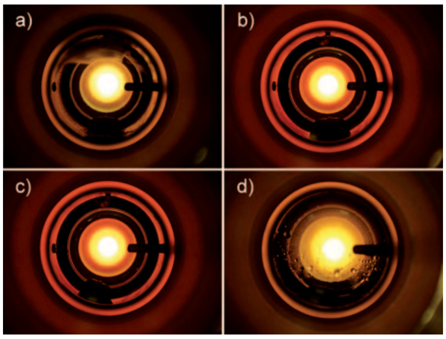


Figure 3. Photographs showing the phase behavior at 55 °C of a mixture containing **3** (5.23 mmol) and DMC (0.0113 mmol) with a mixture of $scCO_2$ (0.432 mol) and N_2 (10.5 mmol) using a variable volume view cell[35] a) 120 bar: multiphase mixture, b) 140 bar: single phase, c) 180 bar: also single phase, d) separate experiment with the product mixture (replacing **3** with the 100 % converted mixture of peroxide products in the same molar ratios). Note the droplets indicating a biphasic mixture with $scCO_2$ under all conditions studied (40–60 °C, 100–200 bar).

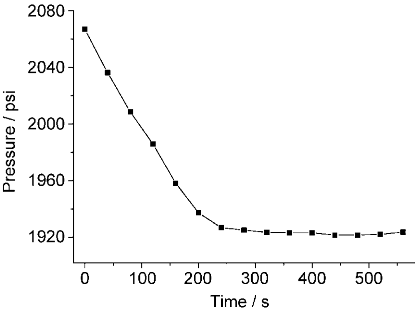


Figure 4. Monitoring the batch photo-oxidation of **3** (0.328 mmol) and DMC (0.709 mmol) with O_2 (0.595 mmol) in $scCO_2$ (2067 psi) at 40 °C. The batch cell was irradiated using a single white 1000 lumen LED. The pressure drop corresponds to one molar equivalent of O_2 being consumed for each mole of **3** present.

phase separation in the reactor did not appear to cause any reduction in the photochemical efficiency. Subsequent acidification of the aqueous phase with HCl was performed overnight and the organic products were extracted with *n*-hexane. GC-MS analysis of the organic phase showed selectivity of 97.6 % **8** (mixture of *cis* and *trans*), 2.2 % **6** + **7**, and 0.2 % **3**.

One of the reasons for choosing **3** is that fairly detailed data are available for the efficiency of the photochemistry in a mulitpass continuous microreactor compared to a conventional Schenk reactor under LED irradiation.[24] According to this analysis, the conventional Schenk reactor with an immersed LED array gave a space–time yield of $0.1\ \text{mmol}\,\text{L}^{-1}\,\text{min}^{-1}$. By contrast a LED illuminated continuous microreactor with a recirculating reaction mixture of 10 mL (0.1 M of **3** in ethanol) gave a space–time yield of $0.9\ \text{mmol}\,\text{L}^{-1}\,\text{min}^{-1}$; that is, nine-times higher than the Schenk reactor. In our system, we have a single pass reactor which is converting 0.27 mmol of **3** per minute with 140 W of electrical input giving a space–time yield of approximately $70\ \text{mmol}\,\text{L}^{-1}\,\text{min}^{-1}$ which is nearly two orders of magnitude higher than the previous microreactor. We can also compare our α-terpinene results with a microfabricated nanoreactor with a 20 W tungsten lamp which gave 80 % conversion in a single pass at a flow rate of $0.0002\ \text{mmol}^{-1}\,\text{min}^{-1}$.[24] By contrast we achieved 100 % conversion at $1.24\ \text{mmol}^{-1}\,\text{min}^{-1}$ an improvement of approximately 6000 times.

Herein, we have described an innovative continuous photocatalytic reactor for performing reactions of $^1O_2$ in $scCO_2$. The reactor has demonstrated the potential of using LEDs for performing synthetic photochemistry in a continuous milliliter-scale reactor with demonstrably higher space–time yields than have been previously observed. This has been accomplished by the combination of high-power LED technology with a high pressure $scCO_2$ reactor system capable of supporting high concentrations of O_2 with negligible mass-transfer limitations.

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