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CO_2-Expanded Solvents: Unique and Versatile Media for Performing Homogeneous Catalytic Oxidations

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Abstract: The work summarized here demonstrates a new concept for exploiting dense phase CO_2, media considered to be “green” solvents, for homogeneous catalytic oxidation reactions. According to this concept, the conventional organic solvent medium used in catalytic chemical reactions is replaced substantially (up to 80 vol %) by CO_2, at moderate pressures (tens of bars), to create a continuum of CO_2-expanded solvent media. A particular benefit is found for oxidation catalysis; the presence of CO_2 in the mixed medium increases the O_2 solubility by ca. 100 times compared to that in the neat organic solvent while the retained organic solvent serves an essential role by solubilizing the transition metal catalyst. We show that CO_2-expanded solvents provide optimal properties for maximizing oxidation rates that are typically 1−2 orders of magnitude greater than those obtained with either the neat organic solvent or supercritical CO_2 as the reaction medium. These advantages are demonstrated with examples of homogeneous oxidations of a substituted phenol and of cyclohexene by molecular O_2 using transition metal catalysts, cobalt Schiff-base and iron porphyrin complexes, respectively, in CO_2-expanded CH_3CN.

Introduction

In the practice of green chemistry,[1−4] the ideal system may be obvious, but practical necessity may require compromise. We show here how such a compromise brings unexpected benefits in a broad family of chemical reactions. For green catalytic oxidations, there is a single truly green oxidant, the O_2 in the air, and since the early 90’s, supercritical carbon dioxide (*sc*CO_2) has been the focus of many studies of “green” homogeneous catalytic oxidations.[5−14] It is recognized that O_2 oxidations in *sc*CO_2 offer maximum environmental benefit, but in many cases *sc*CO_2-based oxidations are limited by low reaction rates, high process pressures (hundreds of bars), and inadequate solubilities of preferred homogeneous catalysts. The most general lesson of the present study is that mixed solvents composed of subcritical CO_2 condensed into an organic solvent provide exciting and unexpected advantages that probably can be extended to many reaction systems.

These solvent mixtures have long been known[19] as CO_2-expanded organic solvents and, for each organic solvent used, entirely new continua of solvents may be generated. De la Fuente Badilla et al. reported experimental data on, and modeled the phase behavior[20] of CO_2-expanded organic solvents, such as acetonitrile, toluene, ethyl acetate, and ethanol. The potential applications of CO_2-expanded solvents in materials processing (such as micro- and nanoparticle formation) and in separation schemes are summarized in a recent review.[21] Here we present the first thorough study of the application of CO_2-expanded solvents to improve a family of chemical reactions, homogeneous catalytic oxidations. In these new kinds of systems the

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organic solvent is substantially (up to 80 vol %), but not totally, replaced by CO_2.

The novel work reported here shows that the O_2 oxidations of phenols, catalyzed by the cobalt Schiff base, Co(salen*), and of cyclohexene, catalyzed by (tetraphenylporphyrinato)iron(III) chloride, in CO_2-expanded CH_3CN, proceed with impressive TOFs (turn over frequencies), conversions, and selectivities. Among the major advantages of using the new solvent media for these reactions are the increased solubilities reported here for O_2 and the catalysts, compared to values in the neat solvents. These results suggest the possible use of CO_2-expanded CH_3CN, and similar media, for a broad range of oxidation reactions since the two catalysts perform oxidations by distinctly different mechanisms.[22]

Experimental Section

Apparatus and Procedures. The volumetric expansion by CO_2 of organic solvents containing dissolved transition metal catalysts is measured in a high-pressure Jurgeson view cell rated to withstand 400 bar at 100 °C. For these expansion studies, a measured volume of organic solution containing a known amount of catalyst (mM) is loaded into the view cell that is equipped with a magnetic stirrer assembly. While monitoring the temperature, pressure and volume of the liquid phase, carbon dioxide is introduced into the cell. Finally at a certain level of expansion and for a given concentration of catalyst, the dissolved catalyst precipitates from the expanded phase. The actual expansion level at which the catalyst precipitates is determined by performing smaller expansions and pressure-releases in the vicinity of the precipitation point. The total volume at which precipitation occurs is registered as the maximum homogeneous expansion level for a solution containing a specific concentration of catalyst (mM) at a certain temperature. Such data are acquired for each solvent/catalyst system at various reaction temperatures and initial catalyst concentrations in order to establish maximum expansion limits with CO_2.

The measurement of oxygen concentrations in CO_2-expanded phases was performed in the same high-pressure view cell used for the volumetric expansion studies. A known amount of solvent is first loaded in the cell. CO_2 is then introduced to expand the solvent to a predetermined level, while simultaneously recording the temperature, pressure, and volume. A predetermined amount of oxygen is slowly bubbled into the liquid phase at the bottom of the cell via a mass flow controller. After equilibration, samples are drawn from the liquid and vapor phases for composition analysis. The composition of the gas phase is determined by GC/TCD analysis. The liquid-phase composition is estimated based on the measured O_2/CO_2 ratio (by GC/TCD analysis) and the measured volume of the expanded phase, assuming that virtually all of the organic solvent resides in the expanded phase. The molar density of the CO_2-expanded liquid phase is estimated from the Peng−Robinson equation of state.

The oxidation studies in CO_2-expanded solvent media were performed in stainless steel stirred batch reactors (10 or 17 mL internal volume). Details of the experimental unit and operating procedures may be found elsewhere.[23] Briefly, each cylindrical cell has end caps fitted with sapphire windows and five ports. Two of the ports are used for introducing O_2 and the solvent medium, CO_2. Oxygen is introduced via a mass flow controller (5860E, Brook Instruments). Liquid CO_2 is pumped to a reservoir and then passed through a bed of anhydrous calcium sulfate (Drierite) to remove any moisture from the CO_2, before introduction into the cell. The third port is used for injecting liquid reactant into the reactor and is connected to a safety head containing a rupture disk. A pressure transducer that continuously monitors the reactor pressure and a thermocouple that monitors the reactor temperature are connected at the remaining two ports. This reactor is designed to withstand pressure and temperature up to 400 bar at 300 °C. A magnetic stirrer provides adequate mixing of the reactor contents. A data acquisition system (Camile TG, Sagian) is employed for continuous controlling and/or monitoring of cell temperature, cell pressure, and O_2 flow rate.

Materials. HPLC grade CH_3CN and CH_2Cl_2, and the catalysts, [{*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)1,2-cyclohexanediaminato(2-)}-cobalt(II)], {i.e., Co(salen*)}, and [{*N*,*N*′-Bis(salicylidene)1,2-cyclohexanediaminato(2-)}cobalt(II)] {i.e., Co(salen)}, were purchased from Aldrich Chemical Co., Inc., and used without further treatment. The substrates 2,6-di-*tert*-butylphenol (DTBP) and cyclohexene were purchased from Aldrich Chemical Co., Inc. Methylimidazole and toluene were purchased from Fisher Scientific and used as received. Coolant grade liquid CO_2 and ultrahigh purity grade oxygen were purchased from Air Products and Chemicals, Inc.

Analysis. A gas chromatograph (HP 5890) with a model 5970 series mass-selective detector was used to identify reaction products. The mass-selective detector was calibrated based on the 28 and 32 amu signals for N_2 and O_2, respectively. The instrument is equipped with a 30 m Alltech RSL-160 column 5μm thick poly(dimethylsiloxane) film, 0.32 mm inside diameter. A gas chromatograph (HP 5890) with FID detector, equipped with the same column, was used for quantitative analysis of reaction products. A gas chromatograph (HP 5890) with TCD detector, equipped with Carboxen-1000, was employed for quantitative analysis of oxygen and carbon dioxide.

Results and Discussion

Catalyst Solubility and Maximum Expansion Limit. In view of the earlier use of CO_2-expansion to precipitate solutes[19−21] and in order to apply CO_2-expanded solvents to homogeneous catalytic oxidations, we have defined and determined the relationships between CO_2-expansion of a conventional solvent, such as CH_3CN, and catalyst solubility in the expanded phase.[24] Isothermal CO_2 addition to a solution of CH_3CN containing a known amount of the dissolved catalyst, [{*N*,*N*′-Bis(3,5-di-*tert*-butylsalicylidene)1,2-cyclohexanediiminato(2)}-cobalt(II)], i.e., Co(salen*), was monitored using the high-pressure Jurgeson view-cell described earlier. The volume of the homogeneous liquid phase increases (i.e., expands) as CO_2 is added, and the catalyst solubility in the expanded solvent decreases continuously until the catalyst precipitates at a certain level of expansion. This point is called the “maximum expansion limit” and is expressed as multiples of the original volume $(V/V_0)_{max}$ (V, volume of CO_2-expanded solvent; V_0, initial volume of neat organic solvent). For a given catalyst/solvent combination, the maximum expansion limit decreases with increasing catalyst concentration and increases with increasing temperature. As shown in Figure 1, at 50 °C for Co(salen*), the 0.33 mM CH_3CN solution has a maximum homogeneous expansion limit of 7 compared to roughly 3.5 for the 1.33 mM solution. For the catalyst concentration employed in our reaction studies (0.66 mM CH_3CN), the maximum expansion limit is roughly 5, also

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[22] In the case of Co(salen*), the somewhat complicated mechanism involves radical formation and combination and in the initial step the bound O_2 moiety abstracts a hydrogen atom from the substrate. In contrast, the iron porphyrin forms high valent iron species that are capable of oxygen atom transfer, as well as one-electron processes.

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[24] The concept of CO_2-expanded solvents is differentiated from the traditional cosolvent concept as follows: cosolvents (typically 1−2 vol %) are added to CO_2 to improve the solubilities of compounds that are poorly soluble in unmodified CO_2. In the case of CO_2-expanded solvents, the organic solvent is the starting point and is significantly replaced by dense phase CO_2. The organic solvent content in the CO_2-expanded phase is on the order of 20−50 vol %, representing a significant reduction in organic solvent usage.

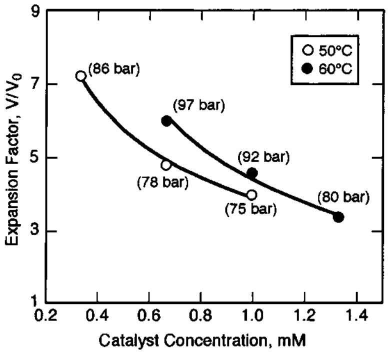


Figure 1. Maximum expansion limits (i.e., without catalyst precipitation) of CH_3CN+Co(salen*) solutions by CO_2. The expansion factor is defined as the ratio of CO_2-expanded solvent volume (V) to the initial solvent volume (V_0 = 5 mL).

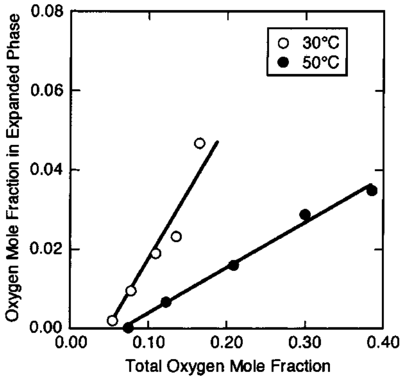


Figure 2. Oxygen mole fraction in the liquid phase of CO_2-expanded CH_3-CN (V/V_0 = 2).

at 50 °C. This implies the possibility of replacing up to 80 vol % of the organic solvent by CO_2 while maintaining the catalyst in solution. It is noteworthy that the total pressures (shown in parentheses in Figure 1) at the maximum homogeneous expansion limit are on the order of several tens of bars. In contrast, higher pressures, on the order of hundreds of bars, are required for solubilizing catalysts in *sc*CO_2; e.g. 345 bar at 80 °C for halogenated iron porphyrins,[9] 207 bar at 70 °C for Co(salen*).[23]

Solubility of O_2 in CO_2-Expanded CH_3CN. The measurements we report here show that another advantage of CO_2-expanded CH_3CN is the higher miscibility of O_2 in CO_2-expanded solvents relative to the neat organic solvents. As shown in Figure 2, the measured O_2 mole fraction in CO_2-expanded CH_3CN ($V/V_0 = 2$) increases approximately linearly with the total oxygen content in the system. As expected, the O_2 solubility decreases at higher temperatures. The O_2 mole fraction in useful levels of CO_2-expanded CH_3CN is about 2 orders of magnitude higher than the O_2 solubility in neat CH_3-CN (mole fraction 5×10^{-4} at 25 °C and 1 bar[25]) and is of the same order of magnitude as that observed in liquid CO_2.[26]

Catalysis by Co(salen*). In the first study of catalytic oxidation by a cobalt(II) oxygen carrier in *sc*CO_2,[23] we showed that the radical mechanism familiar from studies in other solvents applies in this medium. The reaction proceeds via hydrogen abstraction from the phenol, producing the phenoxy radical and the peroxide complex of cobalt(III). The preferred product, the quinone, is formed by oxygenation of the phenoxy radical by a second mole of the O_2 complex. The competing product forms by radical-radical coupling of two phenoxy radicals. In the present work, the catalytic oxidation of 2,6-di-*tert*-butylphenol (DTBP) by Co(salen*) and [{*N,N′*-bis(salicylidene)-ethylenediimino}cobalt(II)], i.e., Co(salen), Scheme 1, was studied in neat CH_3CN, *sc*CO_2, and CO_2-expanded CH_3-CN ($V/V_0 = 2$) in 10 mL stainless steel view cells. We visually confirmed that the Co(salen*) catalyst was completely dissolved in the reaction mixture in all three media. In contrast, Co(salen) was completely dissolved only in the neat solvent and CO_2-expanded CH_3CN. Figure 3 shows that the turnover frequency (TOF), defined as the moles of DTBP converted per mole of dissolved catalyst per hour, in the CO_2-expanded CH_3CN [$V/V_0 = 2$; pressure (p) = 60−90 bar] is between 1 and 2 orders of magnitude greater than that in *sc*CO_2 (p = 207 bar). The observed selectivity toward, 2,6-di-*tert*-butyl-1,4-benzoquinone, DTBQ (80−88%) is comparable in *sc*CO_2 and CO_2-expanded CH_3CN. No CH_3CN oxidation product was detected in either

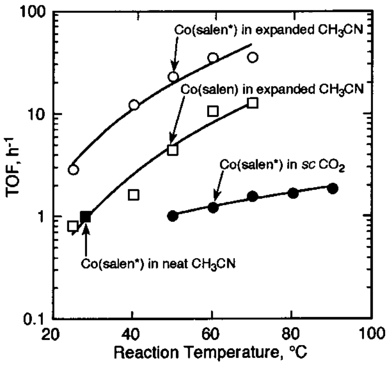
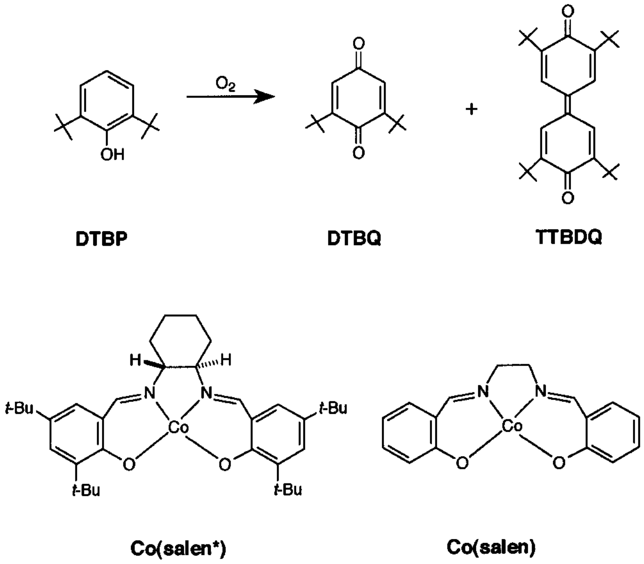


Figure 3. Turnover frequencies (TOFs) for 2,6-di-*tert*-butyl phenol oxidation with Co(salen*) and Co(salen) catalysts at various reaction temperatures. Reaction conditions: total pressure = 1 bar (in neat solvent); 207 bar (in *sc*CO_2) and 50−100 bar (in CO_2-expanded solvent depending on temperature). Catalyst amount = 0.41 μmol, catalyst:substrate:O_2 mole ratio = 1:80:800, volume of methyl imidizole = 2 μL, V/V_0 = 2 (in the case of CO_2-expanded solvent media), reaction volume =10 mL. TOF is defined as moles of substrate converted per mole of dissolved catalyst per hour

Scheme 1. Oxidation of 2,6-di-*tert*-butyl Phenol by Schiff Base Cobalt Catalysts: Co(salen*) and Co(salen)



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neat CH_3CN, or in CO_2-expanded CH_3CN. The TOF and DTBQ selectivity are lower during oxidation in neat CH_3CN that was performed by bubbling O_2 into the liquid phase at near-ambient temperature (28 °C and 1 bar). Higher temperatures with neat solvents can form explosive mixtures in the gas phase and hence were avoided.

The higher TOFs observed in CO_2-expanded CH_3CN (compared to *sc*CO_2) may be attributed to the ability of the polar solvent to stabilize the polar transition state(s), thereby lowering the activation energy and increasing the reaction rate. The rather sensitive temperature dependence of TOFs in the CO_2-expanded phase (over an order of magnitude increase in the 25−80 °C temperature range) relative to that in *sc*CO_2 (2-fold increase in the 50−80 °C range) supports this mechanistic hypothesis. The inexpensive and readily available Co(salen) catalyst shows no measurable DTBP oxidation activity in *sc*CO_2. Interestingly, the Co(salen) also does not dissolve in *sc*CO_2 under the stated reaction conditions. In sharp contrast, Co(salen) shows remarkable activity in CO_2-expanded CH_3CN, with the TOFs being almost an order of magnitude greater than those observed in *sc*CO_2 with Co(salen*), the more active catalyst in traditional solvents (see Figure 3). These results clearly show that CO_2-expanded solvents complement *sc*CO_2 as reaction media by broadening the range of conventional catalyst+solvent combinations with which homogeneous oxidations by O_2 can be performed.

Catalysis by (TPPFeCl). Pioneering studies by Birnbaum, Lacheur, Horton, and Tumas,[9] characterized the oxidation of organic substrates by O_2 under catalysis by fluorinated iron porphyrins. In our work, we exploited the solubility advantages of CO_2-expanded CH_3CN and investigated the oxidation of cyclohexene with a nonfluorinated iron porphyrin catalyst, [chloro(5,10,15,20-tetraphenyl-21*H*, 23*H*-porphine) iron(III)] (TPPFeCl), in addition to a fluorinated catalyst [chloro{5,10,-15,20-tetrakis(pentafluorophenyl)-21*H*, 23*H*-porphine} iron(III)] (PFTPPFeCl). In both cases, molecular oxygen was used as the terminal oxidant. While TPPFeCl is insoluble and displays little activity in *sc*CO_2, it displays remarkably high activity in CO_2-expanded CH_3CN. GC/MS analysis revealed five products: cyclohexene oxide, 1,2-cyclohexane-diol, 2-cyclohexene-1-ol, 2-cyclohexene-1-one, and 4-hydroxy-2-cyclohexene-1-one. While the first two products are those of oxygen atom transfer, the rest are formed by mechanisms that involve allylic H-abstraction.[27] The 1,2-cyclohexanediol is considered to be a product of the subsequent hydration of cyclohexene oxide by moisture present in the system. Therefore, the selectivity toward epoxidation reported herein is based on the yields of both cyclohexene oxide and cyclohexanediol. We investigated conversion histories of cyclohexene oxidation with TPPFeCl at 50 °C in CO_2-expanded CH_3CN ($V/V_o = 2$) and in neat CH_3CN.[5] As shown in Figure 4, in each case, the conversion of cyclohexene to products is associated with an “induction” period. Presumably, this involves the buildup of the concentrations of radicals to the critical level needed to ignite the reaction. Remarkably, the induction period in CO_2-expanded CH_3CN is only 4 h compared to nearly 16 h in neat CH_3CN. We note that this reduced induction period correlates with the enhanced O_2 solubility in CO_2-expanded CH_3CN, suggesting the facilitation of the free radical initiation step involving molecular oxygen.

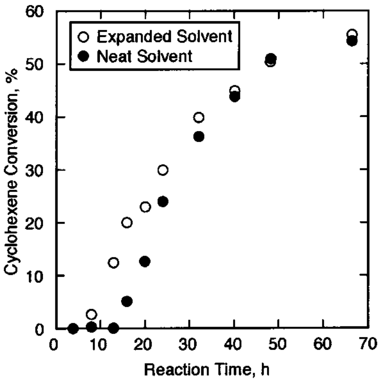

Figure 4. Cyclohexene oxidation in CO_2-expanded CH_3CN and neat CH_3CN. Reaction conditions: temperature = 50 °C, total pressure = 12 bar (neat solvent) and 62 bar (CO_2-expanded CH_3CN), reaction volume = 10 mL, catalyst amount = 2.8 μmol catalyst:O_2:cyclohexene mole ratio = 1:1500:2000, expansion factor (V/V_0) = 2 (for CO_2-expanded CH_3CN).

Table 1. Cyclohexene Oxidation by Iron Porphyrin Complexes in Different Reaction Media[a]

p, bar	reaction medium	*X*, %	*S*, %	catalyst	ref
90	CO_2-expanded CH_3CN	55	19.2	TPPFeCl	this work
90	CO_2-expanded CH_3CN	40.9	28.3	PFTPPFeCl	this work
345	*sc*CO_2	5.5	19	PFTPPFeCl	9

[a] *X*: conversion of cyclohexene. *S*: selectivity toward epoxidation products. Reaction conditions: temperature = 80 °C, time = 4 h, reaction volume = 10 mL, catalyst amount = 2.8 μmol, catalyst:O_2:cyclohexene mole ratio = 1:1500:2000, expansion factor (V/V_0) = 2 (for CO_2-expanded CH_3CN).

Table 1 compares the cyclohexene oxidation results obtained with the nonfluorinated and fluorinated catalysts in *sc*CO_2 and CO_2-expanded CH_3CN. The cyclohexene conversions obtained with the fluorinated catalyst (PFTPPFeCl) in the CO_2-expanded solvent at 90 bar and 80 °C is 41% which is nearly 7-fold greater than that reported by Birnbaum et al.[9] in *sc*CO_2 with the identical catalyst at 345 bar and 80 °C under otherwise similar reaction conditions. Also, an approximately 1.5-fold higher epoxidation selectivity over *sc*CO_2 is obtained in CO_2-expanded CH_3CN. It is interesting to note that the nonfluorinated catalyst (TPPFeCl), which is insoluble in *sc*CO_2, displayed a 10 fold higher TOF for cyclohexene oxidation in CO_2-expanded CH_3CN with comparable epoxidation selectivity.

Concluding Remarks

The foregoing presentation demonstrates, through the example of acetonitrile, that CO_2-expanded solvents constitute a vast array of media that offer endless opportunities for the improvement of chemical reactions. Each CO_2-expandable solvent can, in principle, generate a continuum of media ranging from the neat organic solvent to neat CO_2. Thus, the solvent properties may be varied to accommodate contrasting solubilities simultaneously, like those of oxygen and homogeneous catalysts based on metallic elements; a large amount of CO_2 favors oxygen solubility and polar organic solvents favor metal catalyst solubility. The beneficial physical properties at these limits are elegantly combined in CO_2-expanded reaction mixtures to perform a variety of homogeneous catalytic oxidations of

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organic compounds with a range of transition metal complexes that activate O_2 in different ways. From this and other studies, it appears that most oxidation mechanisms are effective in these solvents.

We have demonstrated several advantages of homogeneous oxidation in CO_2-expanded reaction mixtures. Reaction advantages include higher oxygen miscibility compared to neat organic solvents, applicability to transition metal catalysts without the need for modification (i.e., fluorination) to enhance their solubilities, between one to 2 orders of magnitude greater TOFs and either comparable or better product selectivities than those obtained in neat organic solvent or in *sc*CO_2. Additional significant process advantages accrue at product workup. The catalyst may be separated from the reaction mixture by simply adding more CO_2. The catalyst-free reaction mixture may then be subjected to stepwise pressure reduction to effect the separation of product(s) and remaining reactants.

Environmental and safety advantages are dramatic, including substantial (up to 80 vol %) replacement of organic solvents with dense-phase CO_2, significantly lower process pressure (tens of bars) compared to *sc*CO_2 (hundreds of bars), and with such a substantial presence of CO_2, it is possible to eliminate the formation of explosive mixtures in the presence of oxygen and other potent oxidants. Thus, oxidation in CO_2-expanded solvents is inherently safer when compared to conventional oxidations with traditional solvents.

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