Vanadium-Catalyzed Epoxidations of Olefinic Alcohols in Liquid Carbon Dioxide

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Received June 16, 1999

The selective epoxidation of olefinic alcohols with *t*-BuOOH in the presence of vanadium catalysts proceeds in liquid carbon dioxide with high conversions and selectivities. Rates measured in liquid CO_2 for the oxovanadium(V) triisopropoxide catalyzed epoxidation of allylic and homoallylic alcohols using *tert*-butyl hydroperoxide are comparable to those measured in methylene chloride, toluene, and *n*-hexane. The reactivity of the vanadium(IV) bis(acetylacetonato) oxide catalyst in liquid CO_2 was found to be substantially lower than in organic solvents, presumably due to its low solubility in CO_2. Highly fluorinated acac-type ligands increased the catalytic reactivity of $VO(acac)_2$-catalyzed epoxidations by enhancing catalyst precursor solubility. Heterogeneous epoxidation reactions were also carried out in liquid CO_2 using vanadium complexes supported on cation-exchange polymers.

Introduction

Catalytic selective oxidation of organic compounds continues to be one of the most challenging and important areas of synthetic chemistry.[1,2] Selective oxidation catalysis covers a wide range of chemical transformations ranging from the commodity-scale heterogeneous oxidation of petroleum feedstocks specialized homogeneous transformations with high stereospecificity. Metal-catalyzed homogeneous epoxidations of alkenes are a very useful subset of oxidation reactions, with a rich history that has been described in the literature over the past 30 years.[3] We wish to report the use of dense-phase carbon dioxide as a medium for oxidation catalysis. Dense-phase fluids[4] refer to systems which would be considered gases at their temperature of use but are compressed to the point that they have liquidlike densities ($\rho = 0.3-1.0$ g cm^{-3}). Dense-phase fluids can be used at temperatures above (supercritical fluids) or below (liquid dense-phase fluids) their critical point. The last 5 years have seen a considerable interest in the use of dense-phase CO_2 for catalytic chemistry, motivated by both environmental and reactivity advantages.[5] CO_2 has been reported as a solvent for polymerizations, hydrogenations, hydroformylations, free radical reactions, substitutions, and various other catalytic transformations in both its liquid and supercritical states ($T_c = 30.7$ °C, $P_c = 73.8$ bar). Many of these reports have sought to capitalize on the unique properties of carbon dioxide at supercritical conditions in an attempt to enhance catalysis (e.g., high gas miscibility for hydrogenations).[5] Selective oxidation catalysis has been slower to emerge as a well-studied class of reactions in dense-phase CO_2 despite several properties which make this solvent well suited to oxidations: high oxidative stability, high O_2 solubility, low barriers to mass transfer, and nonflammability.

The earliest oxidation catalysis in dense-phase CO_2 consisted of mainly nonselective, heterogeneous reactions.[6−8] Important contributions in this area include the catalytic oxidation of organics in supercritical (sc) CO_2 using platinum catalysts supported on metal oxide supports by Akgerman and co-workers.[9,10] Dooley and Knopf also studied the oxidation of organics in sc CO_2 but used supported cobalt catalysts with success in demonstrating results similar to those reported in organic solvents.[11] Our work set out to explore the selective oxidation catalysis in dense-phase CO_2 by choosing a well-known reaction, the vanadium-catalyzed epoxidation of several olefinic alcohols using *t*-BuOOH as an oxidant.[2] Reactivities and selectivities, as well as kinetic measurements, were made in organic solvents in order to benchmark reaction rates for a comparison with reactions run in dense-phase CO_2. A preliminary communication of this work has already appeared,[12] which coincided with a report by Kolis and co-workers on the epoxidation of olefins with $Mo(CO)_6$ and *t*-

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(1) *Metal-Catalyzed Oxidations of Organic Compounds*; Sheldon, R. A., Kochi, J. K., Eds.; Academic: New York, 1991.

(2) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63. Chong, A. O.; Sharpless, K. B. *J. Org. Chem.* **1977**, *42*, 1587.

(3) Conte, V.; Di Furia, F.; Licini, G. *Appl. Catal., A* **1997**, *157*, 335.

(4) Morgenstern, D. A.; LeLacheur, R. M.; Morita, D. K.; Borkowsky, S. L.; Feng, S.; Brown, G. H.; Luan, L.; Burk, M. F.; Tumas, W. In *Green Chemistry, Designing Chemistry for the Environment*; Anastas, P. T., Williamson, T. C., Eds.; ACS Symposium Series 626; American Chemical Society: Washington, DC, 1996; p 132.

(5) Jessop, P. G.; Ikariya, T.; Noyori, R. *Chem. Rev.* **1999**, *99*, 475.

(6) Srinivas, P.; Mukhopadhyay, M. *Ind. Eng. Chem. Res.* **1997**, *36*, 2066.

(7) Occhiogrosso, R. N.; McHugh, M. A. *Chem. Eng. Sci.* **1987**, *42*, 2481.

(8) Suppes, G.; Occhiogrosso, R. N.; McHugh, M. A. *Ind. Eng. Chem. Res.* **1989**, *28*, 1152.

(9) Zhou, L.; Akgerman, A. *Ind. Eng. Chem. Res.* **1995**, *34*, 1588.

(10) Zhou, L.; Erkey, C.; Akgerman, A. *Ind. Eng. Chem. Res.* **1995**, *34*, 2122.

(11) Dooley, K. M.; Knopf, F. C. *Ind. Eng. Chem. Res.* **1987**, *26*, 1910.

(12) Pesiri, D. R.; Morita, D. K.; Glaze, W. H.; Tumas, W. *Chem. Commun.* **1998**, *9*, 1015.

10.1021/om990467m CCC: $18.00
Publication on Web 10/28/1999

BuOOH in sc CO_2.[13] After these two publications appeared, there were several reports of selective oxidation catalysis in dense-phase CO_2 ranging from the metalloporphyrin-catalyzed homogeneous oxidation of alkanes and alkenes[14] to the diaestereoselective epoxidation of olefins using salen complexes in sc CO_2.[15]

Herein we provide a detailed study comparing oxidation catalysis in liquid carbon dioxide with that in organic solvents. Reactivities and selectivities as well as kinetic measurements were examined in organic solvents in order to benchmark reaction rates for a comparison with reactions run in dense-phase CO_2. The limited reactivity observed for acetylacetonate (acac)-based catalyst precursors (i.e., $VO(acac)_2$) led to our use of solubility-enhancing ligands to promote epoxidation reactions in CO_2. We have found that fluorinated catalysts are effective in liquid CO_2 and exhibit higher reactivity than unfluorinated systems for certain solubility-limited reactions. Vanadyl cations were also ionically bound to fluorinated and nonfluorinated polymer backbones to heterogenize the epoxidation catalyst in what is believed to be the first report of polymer-supported catalysis in dense-phase carbon dioxide.

Results and Discussion

Epoxidation of Allylic Alcohols. The epoxidation of olefinic alcohols with group V catalysts using alkyl hydroperoxide oxidants was discovered in 1968 by Sheng and Zajacek[16] and concurrently by Kollar.[17] Sharpless and co-workers studied similar systems throughout the 1970s and demonstrated the synthetic utility of metal-catalyzed epoxidations, in part due to their high regio- and stereoselectivity.[18] This class of reactions remains an important tool for synthetic chemists and has been well-studied from a kinetic and mechanistic standpoint. The importance of vanadium-catalyzed epoxidations with alkyl hydroperoxide oxidants, and the understanding that had resulted from three decades of research on these reactions in organic solvents, made this an attractive area of oxidation catalysis to examine in CO_2.

We focused our preliminary experiments on the vanadium(V) catalyst VO(O*i*Pr)$_3$ (oxovanadium(V) triisopropoxide), which was found to be highly soluble in CO_2. This vanadium complex catalyzed the epoxidation of a wide range of allylic and homoallylic alcohols in liquid and supercritical CO_2 using *tert*-butyl hydroperoxide as an oxidant. Reactions at elevated pressure were carried out in custom-built stainless steel high-pressure reactors with sapphire windows to allow for visual observation and with provisions for reagent addition and sampling. These reactors, which have been described elsewhere, can be safely operated at pressures from ambient to 345 bar and temperatures from −40 to 150 °C.[19] Typical epoxidation reactions were run with 1.27 mmol of olefin and 2.4 equiv of *t*-BuOOH in the presence of 3.5 mol % of catalyst and an internal standard in 33 mL of CO_2 by loading the olefin, oxidant, and an internal standard into a glass ampule, which was degassed and flame-sealed. The ampule was placed into the high-pressure reactor inside a glovebox, and the vanadium catalyst was subsequently added to the reactor (outside the ampule). The sealed reactor was then pressurized with CO_2 with the use of a high-pressure manifold, and the ampule was shattered to begin the reaction. The solution was magnetically stirred and was temperature-controlled. Reactions were terminated for analysis by carefully venting the pressurized contents of the reactor into an organic solvent such as ice cold acetone and subsequently rinsing the inside of the reactor with this solution. These oxidations were homogeneous throughout the course of the reaction and resulted in high conversions and selectivities. Reactions were run for 24 h in order to compare conversions and selectivities for different substrates. All preliminary work was carried out at 25 °C (i.e., under liquid-CO_2 conditions) because such oxidations are commonly carried out at or below room temperature in organic solvents and there was no inherent advantage in running these reactions above the critical point (vide infra), as was confirmed by a number of reactions run under supercritical conditions. The results for a number of vanadium-catalyzed epoxidation reactions in liquid CO_2 appear in Table 1.

Conversions and selectivities for a wide range of substrates are shown in Table 1. In general, they were in excess of 90% for the majority of the substrates examined. Yields listed in Table 1 are GC yields.[20] The measured conversions with the VO(O*i*Pr)$_3$/*t*-BuOOH system in liquid CO_2 are consistent with those reported for reactions in organic solvents.[21,22] The epoxidations of *trans*-2-hexen-1-ol (**1**), geraniol (**2**), nerol (**3**), and 1-penten-3-ol (**4**) each exhibited conversions and selectivities above 95%. Although the selectivities for VO(O*i*Pr)$_3$-catalyzed epoxidations of allylic alcohols with *t*-BuOOH in CO_2 were high in most cases, there were a few exceptions. For example, the low selectivity for the aryl-containing cinnamyl alcohol substrate (**8**) was due to a cleavage reaction which formed benzaldehyde as the major product. This result is consistent with literature reports for aryl-substituted olefins.[23] Allyl alcohol

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[13] Haas, G. R.; Kolis, J. W. *Organometallics* **1998**, *17*, 4454.

[14] Birnbaum, E. R.; LeLacheur, R. M.; Horton, A. C.; Tumas, W. *J. Mol. Catal. A* **1999**, *139*, 11. Nu, X.-W.; Oshima, Y.; Koda, S. *Chem. Lett.* **1997**, 1045.

[15] Haas, G. R.; Kolis, J. W. *Tetrahedron Lett.* **1998**, *39*, 5923.

[16] Sheng, M. N.; Zajacek, J. G. Canadian Patent 799 502, 1968.

[17] Kollar, J. U.S. Patent 3 350 422, 1968.

[18] Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136.

[19] Buelow, S.; Dell'Orco, P.; Morita, D. K.; Pesiri, D. R.; Birnbaum, E.; Borkowsky, S.; Brown, G.; Feng, S.; Luan, L.; Morgenstern, D. A.; Tumas, W. *Green Chemistry: Frontiers in Benign Chemical Synthesis and Processing*; Anastas, P. T., Williamson, T. C., Eds.; Oxford University Press: Oxford, U.K., 1998; p 265.

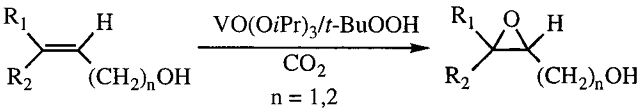
[20] Conversions and selectivities were measured by GC. Conversions were calculated as the percentage of starting material that went on to react (C/C_0), and the selectivity was calculated as the percentage of epoxide with respect to all products formed in a given reaction ($Pi/\Sigma P$). The GC yield can be calculated by multiplying the conversion and selectivity values. The agreement of the GC yields with isolated yields for several reaction products supports the accuracy of this quantification method. For example, both the olefin and epoxide were isolated after the epoxidation reaction of *trans*-2-hexen-1-ol in liquid CO_2. The conversion and selectivity of this reaction in liquid CO_2 were both 99% by GC (a 98% yield). The isolated yield for this reaction, in which the epoxide was isolated as its acetate derivative, was 91%. Epoxide products were isolated using a procedure adapted from that described by Itoh and co-workers.[42] The lower value of the isolated yield is likely to be the result of losses during the isolation but supports the accuracy of the GC yields to within 10%.

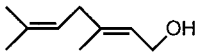
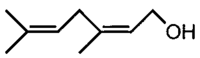
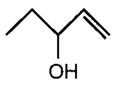
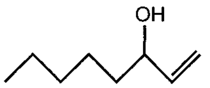
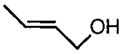
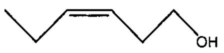
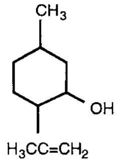
[21] Bartlett, P. A.; Jernstedt, K. K. *J. Am. Chem. Soc.* **1977**, *99*, 4829.

[22] Mihelich, E. D.; Daniels, K.; Eickhoff, D. J. *J. Am. Chem. Soc.* **1981**, *103*, 7690.

[23] Vanadyl acetate catalysts have been reported to cleave styrene analogues to the corresponding aldehyde with yields of 85−98% using H_2O_2 as an oxidant: Choudray, B. M.; Reddy, P. N. *J. Mol. Catal.* **1995**, *103*, L1.

Table 1. Epoxidation of Allylic and Homoallylic Alcohols with VO(O*i*Pr)$_3$/*t*-BuOOH in Liquid CO$_2$[c]



	olefin	P (bar)	Conversion (%)	Epoxide (%)	Yield (%)
1		310	>99	>99	98
2		103	>99	>99	98
3		103	>99	>99	98
4		103	96	>99	95
5		310	>99	>99	98
6		103	53	92	49
7		103	>99	85	84[a]
8		103	>99	20	20[b]
9		103	>99	>99	98
10		103	>99	89	88
11		103	>99	89	88
12		103	89	74	66[a]

[a] Corresponding triol balance of product. [b] 80% benzaldehyde as major product. [c] Reactions were run for 24 h at 25 °C in a 33 mL stainless steel reactor (103 bar). All reactions involved 1.27 mmol of olefin, 3.05 mmol of *t*-BuOOH (as a 5.6 M solution in decane), 44 μmol of catalyst (3.5 mol %), and 91 μmol of octafluoronaphthalene (internal standard). Reactions were depressurized into acetone. Conversions and selectivities were determined by gas chromatography (GC) and products identified with authentic standards (when available) and GC-MS.

(**6**) was the only allylic alcohol tested which did not result in a conversion of greater than 80% (presumably due to limited CO$_2$ solubility of this polar substrate).

With the exception of the sterically hindered isopulegol substrate (**12**), all of the homoallylic alcohol substrates were transformed to their corresponding epoxides with conversions of 99%. The selectivity for the epoxidation of isopugol (**12**) was the lowest (74%), with the triol formed as the predominant side product, apparently from a hydrolysis reaction. *cis*- and *trans*-3-Hexen-1-ol (**10** and **11**, respectively) were both epoxidized with 99% conversion and 89% selectivity, suggesting no effect of the isomer structure on the epoxidation of these olefins, a result consistent with literature reports.

Although there have been no reports of the kinetics of VO(O*i*Pr)$_3$-catalyzed epoxidation reactions, there have been a number of reports of other vanadium catalyst precursors.[3] Since all of these vanadium complexes are likely to be precursors to a common V(V) catalytic species, these reports are relevant to our work. The kinetics of olefin oxidation using vanadium catalysts in organic solvents dates back to the early 1970s, when Sheldon and van Dorn discussed mechanistic details of transition-metal-catalyzed reactions using H$_2$O$_2$ and *t*-BuOOH.[24] Gould and co-workers also reported a kinetic analysis of the vanadium-catalyzed epoxidation

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(24) Sheldon, R. A.; Van Doorn, J. A. *J. Catal.* **1973**, *31*, 427.

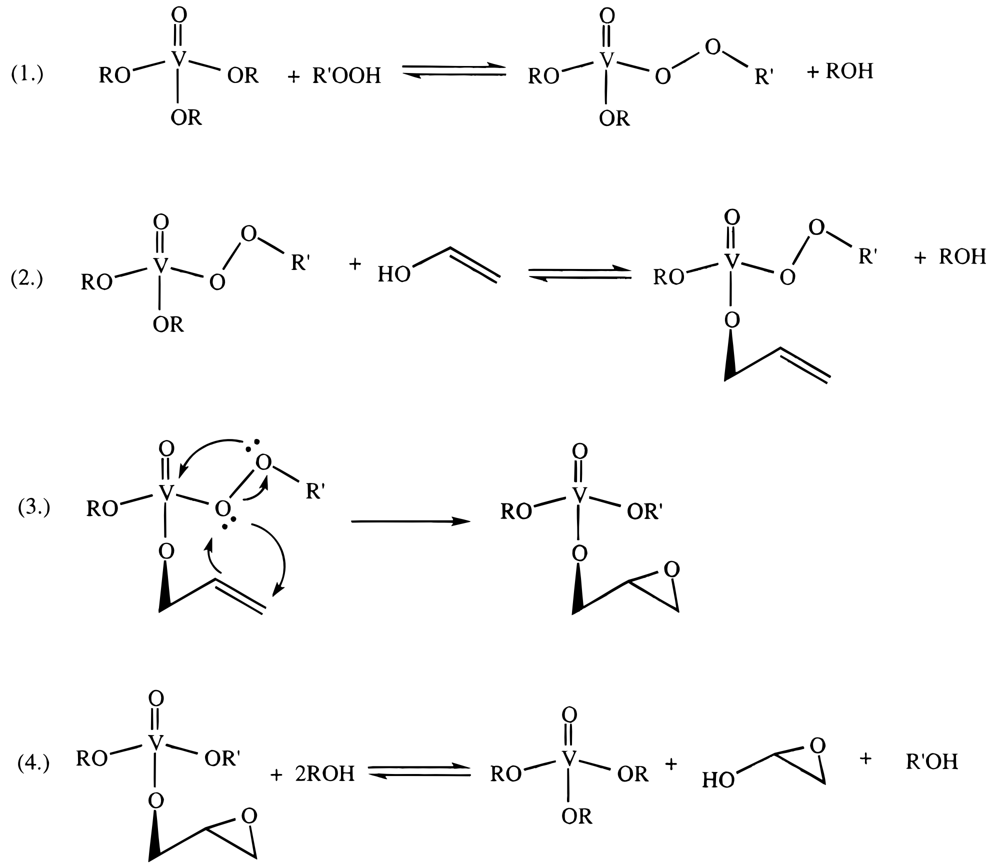

Figure 1. Proposed mechanism for the vanadium-catalyzed epoxidation of allylic alcohols.[2]

of olefins using VO(acac)$_2$ as catalyst precursor.[25] The relative rates of several catalyst systems were reported as well as several important aspects of the reaction mechanism, including the role of *t*-BuOH in inhibiting the epoxidation. More recently, the work of Modena and co-workers has detailed the kinetics of VO(acac)$_2$/*t*-BuOOH-catalyzed epoxidation reactions of olefins in organic solvents in which activation parameters were used to measure the effect of the binding of the −OH group in the transition state.[26] Modena also reported mechanistic details about the epoxidation of geraniol by studying the VO(acac)$_2$-catalyzed oxidation of olefin and thioether substrates.[27] The kinetics of the closely related Ti−tartrate epoxidation catalyst system was reported by Sharpless in 1991 with a detailed study of the kinetic and mechanism aspects of the asymmetric epoxidation of allylic alcohols.[28] The proposed mechanism for the vanadium-catalyzed epoxidation of allylic alcohols is shown in Figure 1. Given the fact that there were no results using VO(O*i*Pr)$_3$ as an epoxidation catalyst in the literature, we set forth to investigate the kinetics of this system in order to benchmark its reactivity. The vanadium-catalyzed epoxidation of *trans*-2-hexen-1-ol and *cis*-3-nonen-1-ol was studied in several organic solvents in order to compare the reactivity in dense-phase CO$_2$. Kinetic experiments were run in a modified version of the high-pressure reactor by fitting it with a high-pressure six-port two-way switching valve, allowing samples to be drawn at high pressures with minimal disturbances to the reaction pressure and volume.[19] When the reaction was carried out with 3.5 mol % catalyst and a 1:1.6 ratio of olefin to *t*-BuOOH, overall first-order kinetics were observed. A linear correlation between reactant concentration and time was obtained by a semilogarithmic plot, which was linear over 4 half-lives (Figure 2).

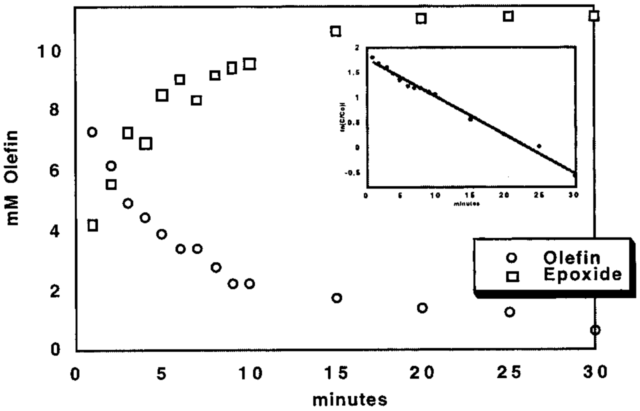

Figure 2. Plot of *trans*-2-hexen-1-ol and 3-propyloxiranemethanol concentrations for epoxidation in liquid CO$_2$ at 24 °C. A first-order fit of the data for the epoxidation appears as an inset.

A rate law was established with respect to olefin, vanadium, and alkyl hydroperoxide by conventional kinetic analysis using a large molar excess of reagents

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(25) Gould, E. S.; Hiatt, R. R.; Irwin, K. C. *J. Am. Chem. Soc.* **1968**, *90*, 4573.

(26) Bortolini, O.; Di Furia, F.; Modena, G. *J. Mol. Catal.* **1982**, *16*, 61. Bonchio, M.; Conte, V.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1989**, *54*, 4368.

(27) Cenci, S.; Di Furia, F.; Modena, G. *J. Chem. Soc., Perkin Trans. 2* **1978**, 979.

(28) Woodard, S. S.; Finn, M. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 106.

to achieve “constant” concentrations for the remaining reagents. When the concentration of olefin was doubled with a large molar excess of both oxidant and catalyst, the rate constant doubled, confirming a first-order dependence on olefin. Similar results were obtained for experiments establishing the order of the reaction with respect to *t*-BuOOH and catalyst, confirming that the reaction is nearly first order for all three.[29] A fourth term is present in the rate law and corresponds to an inverse dependence of *t*-BuOH, the reduced product of *tert*-butyl hydroperoxide. This nonintegral denominator likely arises from a term such as $k_a + k_b[t\text{-BuOH}]$, which describes the inhibitory role of *tert*-butyl alcohol in the mechanism's ligand dissociation step. An expression for the measured rate law appears in eq 1.

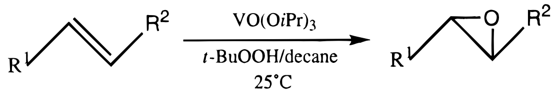
$$\text{rate} = \frac{-\text{d[olefin]}}{\text{d}t} = \frac{\text{[epoxide]}}{\text{d}t} = \frac{k[\text{olefin}]^{1.0}[t\text{-BuOOH}]^{0.95}[\text{VO(O}i\text{Pr)}_3]^{0.98}}{[t\text{-BuOH}]^{0.4}} \qquad (1)$$

At the initial reaction times used for our kinetic studies, the dominance of the k_a term in the denominator (i.e. low [*t*-BuOH]) simplifies the rate law to the form expressed in eq 1. This rate law is consistent with that proposed for the epoxidation of allylic alcohols by group V metal centers in which olefin, oxidant, and catalyst are each involved in a prebinding step that forms the active catalytic species.[2] An intramolecular oxygen atom transfer from the bound *t*-BuOOH to the olefin results in a bound epoxide and the reduced *t*-BuOH group. Subsequent displacement of the product and alcohol by olefin and 1 equiv of *t*-BuOOH completes the catalytic cycle.

Rate constants were calculated for the epoxidation of allylic and homoallylic alcohols in the following manner. Apparent first-order rate constants, k (min^{-1}), were obtained from plots of ln(C/C_0) vs time for the disappearance of olefin. These values were then converted into second-order rate constants (s^{-1} M^{-1}) to give k'. At the low levels of *t*-BuOH during initial conditions the effect on the rate can be excluded from the calculation of k'. Rates of epoxidation for two olefins in liquid CO_2 and several organic solvents are listed in Table 2. The rate constant, k', for *cis*-3-nonen-1-ol in CO_2 was determined to be 9 s^{-1} M^{-1}, and the rate for the epoxidation of *trans*-2-hexen-1-ol was 146 s^{-1} M^{-1}at 25 °C.

The reaction rate in CO_2 is 3 times that in hexane and roughly equal to that in carbon tetrachloride for the homoallylic alcohol substrate. Reaction rates for this substrate were measurably greater in dichloromethane, acetonitrile, and toluene. The trend in reaction rates was similar for the *trans*-2-hexen-1-ol substrate: dichloromethane, acetonitrile, and toluene reactions were faster than those in CO_2. The epoxidation of the allylic alcohol in CO_2 was faster than in tetrahydrofuran. Methylene chloride gave the highest rates for epoxidation reactions of both allylic and homoallylic alcohols. The superiority of chlorinated alkanes as solvents for metal-catalyzed epoxidations has been reported by Sheldon.[30] In general, however, there was not a large rate dependence on the solvent, a result not unexpected for such a nonpolar, nonionic reaction. The rate of allylic alcohol epoxidation using VO(O*i*Pr)$_3$ was higher that that for homoallylics, a result consistent with literature reports that claim allylic alcohols react roughly 5 times faster than homoallylic alcohols during epoxidation with vanadium and titanium catalysts.[31] The data in Table 2 suggest that carbon dioxide does not inhibit the rate of the vanadium-catalyzed epoxidation reaction; rather, the rates are roughly in line with the polarity of the solvent for both allylic and homoallylic alcohols. The solubility and reactivity properties of dense-phase CO_2 are commonly compared to those of alkanes such as pentane and hexane, but these results suggest that toluene or carbon tetrachloride may be a better model for reactivity in CO_2, particularly for nonpolar reactions.

Table 2. Rate of Homoallylic Alcohol Epoxidation in Various Solvents at 25 °C[a]



	$R^1 = C_5H_{12}$, $R^2 = C_2H_4OH$[b]		$R^1 = C_3H_7$, $R^2 = CH_2OH$[c]	
solvent	k' (s^{-1} M^{-1})	k_{rel} (CO_2)	k' (s^{-1} M^{-1})	k_{rel} (CO_2)
dichloromethane	30	3.3	252	1.7
acetonitrile	18	2.0	176	1.2
toluene	17	1.9	158	1.1
carbon dioxide	9	1.0	146	1.0
carbon tetrachloride	5	0.6		
n-hexane	3	0.3		
tetrahydrofuran			34	0.2

[a] Initial observed first-order rates were converted to second-order rate constants. All reactions were carried out at 24 ± 0.1 °C. Rates measured in CO_2 were carried out at 29 bar in high-pressure reactors. Reactions involved [VO(O*i*Pr)$_3$] = 1.47 μM (3.5 mol %), [*t*-BuOOH] = 100 mM, and [olefin] = 42 mM. Rates reported are accurate to 10%. Activation parameters for the epoxidation of *trans*-2-hexen-1-ol were 3.6 kcal mol^{-1} and −35 eu for ΔH and ΔS, respectively. ΔH and ΔS values for *cis*-3-nonen-1-ol were 2.5 kcal mol^{-1} and −38 eu, respectively. The enthalpies of activation for both reactions were lower than those in literature reports for cyclohexene epoxidation using VO(acac)$_2$. [b] *cis*-3-Nonen-1-ol. [c] *trans*-2-Hexen-1-ol.

Several experiments under liquid and supercritical CO_2 conditions revealed that pressure had no measurable effect on the conversions or the selectivities of these reactions, a result not surprising in such a high-density (liquid CO_2) regime. For example, at 103 bar and 25 °C the rate from Table 2 for the epoxidation of *trans*-2-hexen-1-ol is 146 s^{-1} M^{-1}. At the same temperature and a pressure of 345 bar the rate of the reaction is 151 s^{-1} M^{-1}. Under liquid CO_2 conditions (T = 25 °C) there appears to be no difference between the rates within experimental error. When the same reaction was run at 35 °C and 103 bar (above the critical point), the reaction rate was 382 s^{-1} M^{-1}. A pressure increase to

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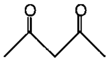
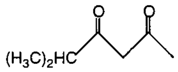
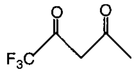
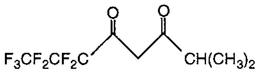
(29) A practical limitation was encountered with the use of *t*-BuOOH as an anhydrous 5−6 M solution in decane. Reactions that required a large excess of *t*-BuOOH were run with reduced quantities of olefin and catalyst to avoid unacceptably high decane levels in the CO_2. It is important to point out that cosolvents in dense-phase fluids have been shown to have a potentially large effect on the dense-phase media's properties and the extent of this effect, even at levels below 10%, may be worthy of investigating.

(30) Sheldon, R. A.; Van Doorn, J. A.; Schram, W. A.; De Jong, A. J. *J. Catal.* **1973**, *31*, 438.

(31) Dehnel, R. B.; Whitman, G. H. *J. Chem. Soc., Perkin Trans. 1* **1979**, *4*, 953.

Table 3. Epoxidation of *trans*-2-Hexen-1-ol Using Substituted VO(acac)$_2$ Ligands[a]

ligand	P (bar)	(%) Conversion	(%) Selectivity
	103	64	89
	103	91	95
	103	99	98
	103	99	99

[a] Reactions were run for 6 h at 24 °C in 33 mL high-pressure reactors. Each experiment used 3 mmol of olefin, 4 mmol of *t*-BuOOH, and 75 μmol of catalyst.

345 bar at 35 °C resulted in a rate of 385 s^{-1} M^{-1}. The effect of pressure on the epoxidation reaction above the critical point was negligible. Clearly these reactions are not in the mass-transfer-limited regime. The lack of any measurable pressure effect or any benefits in carrying out these reactions above room temperature led to the majority of these reactions being carried out under liquid-CO_2 conditions.

VO(acac)$_2$. VO(acac)$_2$ is known to be one of the most effective epoxidation catalysts in organic solvents. We did not observe high conversions in preliminary experiments using VO(acac)$_2$ in dense-phase CO_2, however. Reactions with VO(acac)$_2$ were turbid and contained a precipitate, suggesting poor solubility. In an attempt to enhance the activity of the vanadium acetylacetonate complex we examined fluorinated, less polar acetylacetonate analogues which would impart higher solubility in dense-phase CO_2.

The use of highly fluorinated structures to improve chemistry in supercritical CO_2 has been reported by several researchers for reactions ranging from hydroformylations[32] to metalloporphyrin-catalyzed autoxidations.[14] Leitner and co-workers increased the CO_2 solubility of catalysts to improve chemical transformations with modified catalysts which incorporate perfluoroalkyl substituents to enhance solubility (and reactivity) in sc CO_2.[32] This example of a widely used ligand system which was modified to improve its reactivity in dense-phase CO_2 may expand the field of homogeneous catalysis in sc CO_2 by overcoming solubility limitations. Holmes and Carroll[33] as well as Tumas and co-workers[34] have also demonstrated the effectiveness of fluorinated substituents on catalyst complexes for palladium-catalyzed carbon−carbon bond-forming reactions in supercritical CO_2.

Oxidation catalysis using fluorinated ligands for increased reactivity in organic solvents actually dates back three decades. In 1968 Gould and co-workers studied the vanadium-catalyzed epoxidation of cyclohexene using VO(acac)$_2$ and *t*-BuOOH.[35] This report also included reaction rates for vanadium-catalyzed epoxidations of olefins using fluorinated acetylacetonates with increased reactivity. Our experiments involved the use of commercially available fluorinated acac compounds, including 1,1,1-trifluoro-2,4-pentanedione (tfac), 6,6,7,7,8,8,8-heptafluoro-3,5-octanedione (hfac), and 5,5-dimethylhexane-2,4-dione (dmac), to prepare catalyst precursors by binding them to vanadyl salts in aqueous solutions to form VO(acac)$_2$ complexes according to literature methods.[35]

The results from Table 3 demonstrate that increasing the catalyst solubility increases the reactivity. The highest conversion achieved for the VO(acac)$_2$-catalyzed epoxidation of *trans*-2-hexen-1-ol in liquid CO_2 was 64% at 24 °C with a selectivity of 89% in 6 h. The presence of two methyl groups on the acac ligand increases the conversion of this reaction to 91%. A further increase in the conversion resulted when a fluoromethyl or fluoroalkyl plus methyl was substituted on the acac. The low conversion in the reaction with the unsubstituted acetylacetonate ligand is likely attributable to observed precipitates in the liquid CO_2, an indication of limited solubility. The relative rates for the epoxidation of *trans*-2-hexen-1-ol using the difluoromethyl-substituted acac ligand was 7.6×10^{-3} s^{-1}, compared to 5.3×10^{-3} s^{-1} for the unsubstituted acac in CO_2. Both the fluoromethyl- and fluoroalkyl-substituted acetylacetonate ligands gave rates of 1.7×10^{-2} s^{-1} in liquid CO_2. These reactions were again roughly 3 times slower than reactions run in dichloromethane under identical conditions. The similarity in the initial rates of reactions which exhibit different conversion levels is analogous to a published report of palladium-catalyzed cross-coupling reactions using several phosphine ligands.[33,34] The higher conversions in both cases appear to arise from catalyst solubility and suggest the substituted acac's role in enhancing the conversion is due to an improvement in the CO_2 solubility of the vanadium complex.

Polymer-Supported Vanadium Catalysis in Liquid CO_2. The concept of attaching homogeneous catalysts onto fixed organic or inorganic supports to offer the separation advantages of a heterogeneous system has received a great deal of attention during the past two decades. For example, a number of researchers have explored the potential for polymers to act as heteroge-

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(32) Kainz, S.; Koch, D.; Baumann, W.; Leitner, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1628.

(33) Carroll, M. A.; Holmes, A. B. *Chem. Commun.* **1998**, *13*, 1395.

(34) Morita, D. K.; Pesiri, D. R.; Glaze, W. H. *Chem. Commun.* **1998**, *13*, 1397.

(35) Su, J. C.; Reed, J. W.; Gould, E. S. *Inorg. Chem.* **1973**, *12*, 337 and references therein.

neous supports for catalytic transformations,[36] including a number of vanadium-catalyzed epoxidations.[37] We were intrigued by the idea of using anionic polymers as supports for cationic vanadyl cations for epoxidations in dense-phase CO_2. Two important aspects of polymer-supported catalysis in dense-phase CO_2 which compelled our investigation were the extreme nonplanarity (and correspondingly low solvation power) of CO_2, making the leaching of cationic catalysts less favorable, as well as the potential for CO_2 to swell certain polymer structures. We studied cationic vanadyl species ionically exchanged onto anionic sites of two different polymer structures, the commercially available Nafion (a perfluoronated alkane backbone with sulfonate functionality), and Amberlite IRC50 (a polystyrene backbone with carboxylate functionality).

The two polymer-supported catalysts were examined for the epoxidation of *trans*-2-hexen-1-ol in liquid CO_2. A Nafion-supported catalyst had a reaction rate ($k_{obs} = 0.015\ s^{-1}$) that was lower than that of the corresponding homogeneous reaction using $VO(OiPr)_3$ in liquid CO_2 ($0.126\ s^{-1}$). The lower rates for polymer-supported catalysts are likely due, in part, to a lower catalyst loading. Reaction rates for the polymer-supported and homogeneous reactions were equal when corrected for catalyst concentration. The Nafion-supported catalyst gave a conversion of 80% with a very low selectivity (21%) during a 6 h reaction. Extraction experiments identified the majority of products to be oligomeric species intimately associated with the polymer backbone. The oligomer was the result of a ring-opening reaction at the Lewis acidic sulfonate sites on the polymer. To avoid the reactivity of the Lewis acid polymer structure, an Amberlite-supported catalyst was used for the epoxidation of *trans*-2-hexen-1-ol. Although it exhibited a slightly lower reaction rate than the Nafion system ($k_{obs} = 0.0085\ s^{-1}$), the epoxide product was found to be stable. Conversions of 90% and selectivities of epoxide of over 95% were achieved with this system. Although epoxidation reactions were shown to proceed using polymer-supported vanadium catalysts in liquid CO_2, the degree of catalyst leaching was significant (greater than 3% of the catalyst loading leached over a 6 h reaction).

Conclusions

Our results clearly indicate that selective oxidation reactions can be carried out in liquid CO_2. The high selectivities and conversions achieved in several vanadium-catalyzed epoxidation reactions in liquid carbon dioxide are important evidence that this medium does not limit the catalytic activity of electrophilic, peroxidic transition-metal catalysts. In virtually every case the epoxide yield was comparable to reactions run in organic solvents such as *n*-hexane, methylene chloride, and toluene. Rates measured for $VO(OiPr)_3$-catalyzed epoxidation of olefinic alcohols fall squarely in the range of the organic solvent reactions examined. This result suggests the validity of considering dense-phase CO_2 as a potential organic solvent alternative for homogeneous catalytic oxidation transformations. In the case of the $VO(acac)_2$-catalyzed epoxidation of allylic alcohols, limited solubility of the catalyst or catalyst precursor limited the reactivity. The use of highly fluorinated analogues of the acetylacetonato ligands did increase the reactivity of this system in what is believed to be the first demonstration of enhanced oxidation catalysis in a dense-phase fluid through improvements in catalyst solubility. Ion exchange polymer supports did not offer any significant control over vanadium catalyst leaching for epoxidation reactions in liquid CO_2, however. While the reaction rates are similar in liquid CO_2 and organic solvents, a result that is not surprising for a nonpolar reaction, we believe that other selective oxidations deserve further investigation. The opportunity for enhanced catalysis in dense-phase carbon dioxide warrants an exploration of reaction systems that capitalize on the unique properties favoring oxidation chemistry.

Experimental Section

High-Pressure Batch Reactions. All high-pressure reactions were carried out in specially designed, custom-built 316 stainless steel reactors with sapphire windows to allow visual inspection at high pressure. These reactors have been described in detail elsewhere.[4,19] In addition to the window flange, these reactors were fitted with a pressure gauge, inlet and outlet valves, a rupture disk, and a thermocouple. Reactions were mixed with Teflon stirbars in situ using magnetic stirplates. Glass ampules were used in all high-pressure reactions as a means of introducing reagents and catalyst. Constant temperatures of up to 90 °C were achieved with heating tape wrapped around the outside of the reactor with control through a temperature controller (Omega). A typical epoxidation reaction with $VO(OiPr)_3$ and *t*-BuOOH involved loading the olefin (1.27 mmol), 2.6 equiv (3.3 mmol) of a 5−6 M solution of anhydrous alkyl hydroperoxide in decane (Aldrich), and octafluoronaphthalene (92 μmol, used as an internal standard, Aldrich) into a 2 mL glass ampule which was degassed (freeze−thaw cycling), flame-sealed under vacuum, and placed in the reactor. *tert*-Butyl hydroperoxide was obtained as a 5−6 M solution in decane (Aldrich). All reagents were used as purchased, without further purification. The peroxide solution was assayed for *t*-BuOOH using a titration method published by Sharpless.[38] Alkyl hydroperoxides were found to be soluble in both liquid and supercritical CO_2 (>23% v/v) and were used in all of the epoxidation experiments. Vanadyl triisopropoxide catalyst (44 μmol, 0.035 mol %, Strem) was then added to the reactor in a glovebox. A sealed ampule containing the balance of reactants and a dry stirbar were also added to the reactor in the glovebox. The reactor was then hand-tightened at the window flange using Teflon O-rings on each side of the sapphire window. The reactor was removed from the glovebox, tightened by wrench, and pressurized using a high-pressure manifold system inside a fume hood. Ultra-high-purity carbon dioxide (Matheson) was passed through purification columns (an oxygen trap (Alltech), charcoal trap (Alltech), a moisture trap (Alltech), and 8 Å molecular sieves) to ensure purity. Upon pressurization with CO_2, the ampule imploded, resulting in the mixing of the catalyst with reagents, marking the beginning of the reaction. Hydrostatic pressures of 103 bar were chosen for liquid-CO_2 reactions because this is above the vapor pressure of CO_2 (60.6 bar) at 25 °C and results in homogeneous solutions in a single liquid-CO_2 phase in the pressure cell. At 25 °C, pressures between 61 and 76 bar result in a two-phase system with condensed (liquid) CO_2

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in contact with a CO_2 vapor above it. Two-phase reaction conditions are sometimes desirable due to the low pressures associated with these liquid-CO_2 reactions, but the presence of the liquid- and vapor-CO_2 phases can introduce complications in homogeneous catalysis reactions due to uncertainty in reaction volumes. In summary, liquid-CO_2 pressures of 103 bar were chosen as the lowest possible pressure that was still safely in the single-CO_2-phase region.

Batch reaction contents were collected by venting the CO_2 pressure into a glass vial filled with an organic solvent (20 mL of acetone, hexane, or ethyl acetate). Routine analyses were accomplished by gas chromatography (GC) using a Hewlett-Packard 5890 Series II instrument with FID detector and 30 m capillary (1.5 μm i.d.) DB 624 column (Alltech). Calibration curves with commercially available standards were used when available to quantify conversions and selectivities. Reaction products were identified using a Hewlett-Packard 5971 A instrument with mass-selective detector (GC MS) and 30 m capillary DB 624 column (1.5 μm i.d.) as well as ^{1}H and ^{13}C NMR for isolated products with and without derivatization.

Kinetics. Kinetic experiments in CO_2 were carried out in identical 33 mL stainless steel reactors which had been modified for sampling. A Hastelloy high-pressure (344 bar) six-port two-way switching valve (Valco Inc.) was used to take samples from the reactor at high pressure. A 100 μL sample loop was used in all experiments to provide a uniform sample size. The contents of the loop were vented into a dry 1.8 mL glass GC vial, the loop was rinsed with solvent via syringe, and the rinsing solution was collected in the same GC sample vial. The vial was then sealed and analyzed directly by GC. The use of an internal standard enabled quantitative analysis of the olefin and epoxide with good reproducibility and accuracy. Reactions in organic solvents were carried out in 100 mL glass three-necked round-bottom flasks fitted with a condenser. Molecular sieves (4 Å, 8−12 mesh, ca. 100) were added, and VO(O*i*Pr)$_3$ catalyst was added via syringe to the flask. The round-bottom flask was connected to nitrogen via a Schlenk line. Samples were taken via a syringe needle and were quenched with acetone and analyzed by GC. The epoxides were difficult to isolate directly; therefore, their acetate derivatives were prepared for isolation by the method described by Itoh and co-workers.[39] Second-order rate constants were calculated by dividing the apparent first-order rate constant by 60 (seconds per minute) and by the concentrations of catalyst (3.9×10^{-3} M), *t*-BuOOH (136 mM), and olefin (48 mM) to give k'.

Preparation of the Fluorinated Vanadium−Acetylacetonate Complexes. Literature methods were used for the synthesis of the vanadium complexes of the fluorinated acetylacetonate ligands.[35] Vanadyl trifluoroacetylacetonate (VO(tfac)) was prepared by dissolving 1.0 g of $VOSO_4{\cdot}4H_2O$ (Strem) in 5 mL of deionized water, adjusted to pH 3 with the addition of aqueous Na_2CO_3, followed by the addition of 1.6 mL of 1,1,1-trifluorohexane-2,4-dione. During the addition of the ligand the pH was kept at 3.0 with the addition of a 5% aqueous Na_2CO_3 solution. The mixture of green and white precipitates was filtered and washed with deionized water to remove white precipitate, and the crude green product was recrystallized from benzene and dried under vacuum. The product was stored cold, under N_2. Vanadyl dimethylacetylacetonate was also prepared by this aqueous method, in which 1 g of $VOSO_4{\cdot}4H_2O$ and 250 μL of 5,5-dimethylhexane-2,4-dione were combined at pH 3.0. The complex was recrystalized from benzene and dried as above. Vanadyl heptafluorodimethylacetylacetonate could not be obtained in high yield with the previous method; therefore, a procedure in which 1 g of V_2O_5 was added to 4 mL of ethanol and 5 mL of water with 0.5 mL of concentrated H_2SO_4 was used.[40] This solution was heated to 75 °C for 20 min, at which time the precipitate was filtered. To the filtrate was added 1 g of 2,2-dimethyl-6,6,7,7,8,8,8-heptafluoro-3,5-octanedione (Aldrich) dropwise. The mixture was then neutralized with 5% Na_2CO_3 to precipitate the complexes, which were recrystallized from benzene and dried in vacuo over P_2O_5.

Acetylation of Allylic and Homoallylic Alcohols and Epoxy Alcohols. The epoxides were difficult to isolate directly; therefore, their acetate derivatives were prepared for isolation in the following manner. The reactor contents were depressurized and collected in 20 mL of acetone, and this solution was then used to rinse the reactor as described earlier. The acetone solution was then concentrated by rotovaporation at room temperature to roughly 5 mL. The acetylation was carried out by adding 1.5 mmol of triethylamine, 1.5 mmol of acetic anhydride, and 0.08 mmol of 4-(dimethylamino)pyridine for every 1 mmol of analyte to be derivatized. The deep yellow solution was stirred in a 100 mL round-bottom flask, during which time the acetylation solution turned a deep gray-green color and evolved a significant amount of heat. The reaction was complete within 6 h. The entire solution was diluted with 10 mL of diethyl ether and washed in a 250 mL separatory funnel with 1 M HCl (1 × 20 mL). The acetlyation products were then extracted with an additional volume of 20 mL of diethyl ether. The organic layer was subsequently washed in succession with saturated aqueous solutions of the following: $NaHSO_3$ (1 × 15 mL), $NaHCO_3$ (1 × 20 mL), and NaCl (2 × 20 mL). The acetylated product was dried over $MgSO_4$ and filtered using filter paper and a glass wide-mouth funnel. The organic filtrate was concentrated in vacuo using a rotavap, yielding an oil which was transferred to a sealed Schlenk storage flask. Thin-layer chromatography with 1:1 hexane−ethyl acetate gave good separation of the products with an acceptable R_f value. The acetylated product was separated by flash chromatography. A 62 cm glass column, 2.5 cm width (Aldrich), was filled with silica gel (Merck, grade 9385, 230−400, mesh 60 Å). Roughly 5 mL of the acetylated oil was added to a sea sand plug at the top of the column, and the hexane−ethyl acetate mobile phase was forced through with a flow rate of approximately 5 mL/min. Ten milliliter fractions were collected and stored. Each fraction was analyzed by GC-MS, and those containing pure acetylated product were combined and concentrated in vacuo by rotavaporation. The pure product (as an oil) was weighed and a portion solubilized in acetone for GC-MS analysis; another portion was solubilized in benzene-d_6 for ^{1}H NMR analysis. The analysis of the acetylated product confirmed the presence of high-purity material.

Polymer-Supported Catalysis. Nafion-Na$^+$ (purchased as Nafion-H$^+$ as Nafion NR 50 beads, Aldrich) was washed in a solution of pH 5 aqueous NaOH (200 mL, 0.05 mol NaOH) and stirred until the pH dropped to a constant level. The beads were washed in deionized water, and the NaCl washing process was repeated. The beads were then washed a third time with a stronger NaCl solution (200 mL, 0.7 mol NaOH) and washed once the pH leveled off. Nafion-K$^+$ was prepared using an identical method involving KOH. Vanadium was exchanged onto the polymer in several different solvents, including water, methanol, and 2-propanol. These methods were evaluated, and the most effective was determined to use vanadyl sulfate ($VOSO_4{\cdot}3H_2O$, Fisher) because of its simplicity (other methods required inert atmospheres) and stable vanadyl−polymer product. Quantification of the vanadium on the polymer support was achieved by analyzing the preparation solution after the exchange and subtracting the difference from the quantity added at the beginning of the reaction. This method of subtraction required an accurate quantification of the hydrated vanadium salt added to the exchange solution. The hydration number of the $VOSO_4$ was measured by dissolving 0.1 g of $VOSO_4$ (Fisher Lot No. 964622) in 30 mL of

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(40) Rowe, R.; Jones, M. M. *Inorg. Synth.* **1957**, *5*, 114.

deionized water. ICP analysis of vanadium yielded a concentration of 742 μg of V/g of solution, or 0.003 473 mol of vanadium/g of $VOSO_4{\cdot}nH_2O$, where $n = 4.93$. This hydration number was constant over time and was used in all vanadium sulfonate measurements. The vanadyl cation was exchanged with the Nafion-Na by combining Nafion-Na (12 g) with a solution of vanadyl sulfate in deionized water (830 mg of $VOSO_4$, 100 mL of H_2O). This aqueous mixture was stirred while the concentration of vanadium was followed by UV−vis spectroscopy. When the concentration in solution indicated the desired vanadium loading on the polymer, the beads were filtered and rinsed with deionized water. The dried beads were sealed under an atmosphere of argon to prevent deactivation (exposure of the Nafion beads to air turned them a black-brown color and inactivated them). Amberlite exchange with VO^{2+} was accomplished in an identical manner. Leaching studies were carried out in hexane as an analogue to CO_2. The loading of vanadium on a typical polymer was 0.1656 g of V/g of Amberlite IRC 50. Polymer-supported catalytic reactions were run by adding octafluoronaphthalene (0.09 g, internal standard) and the catalyst beads (equivalent of ∼0.009 mmol of vanadium) to the high-pressure batch reactor. *tert*-Butyl hydroperoxide (7:1 molar ratio of tBHP to *trans*-2-hexen-1-ol) and *trans*-2-hexen-1-ol (2.1 mmol) were added to a glass ampule that was evacuated, sealed, and added to the reactor. Kinetic analyses were performed in a manner identical with that described for $VO(O\textit{i}Pr)_3$-catalyzed reactions.

Safety Note. There are inherent risks in conducting reactions at elevated pressures, although the danger can be managed with the appropriate design and procedural practices. No research of this type should be conducted in the absence of the necessary safety precautions. All reactions were carried out in a fume hood which was modified with $^1/_2$ in. polycarbonate blast shielding. Reactors at high pressures were fitted with pressure relief valves or rupture disks and were fixed into place with a steel framework to reduce the risk of personal injury.[4141]

Acknowledgment. This work was supported as part of the Los Alamos Catalysis Initiative by the Department of Energy through a Laboratory Directed Research and Development (LDRD) grant and a grant from the U.S. EPA, Office of Pollution Prevention and Toxics (Grant Number 1877-97-1). We acknowledge many helpful discussions with R. Tom Baker, William Glaze, and Steve Buelow. We also thank Phil Dell'Orco for assistance on preliminary polymer support work.

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