Selective epoxidation in dense phase carbon dioxide

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Selective epoxidations with transition metal catalysts (V, Ti, Mo) and Bu^{t}OOH proceed with high conversions and high selectivity in dense phase carbon dioxide.

The selective catalytic oxidation of olefins constitutes one of the most fundamentally important classes of synthetically useful reactions and is typically carried out in aromatic or chlorinated hydrocarbon solvents.[1,2] We report here the first demonstration that dense phase carbon dioxide‡ is an effective solvent for the selective oxidation of activated alkenes using Bu^{t}OOH and a number of transition metal catalysts. High valent oxovanadium(V) tri(isopropoxide) [VO(OPr^i)$_3$] with Bu^{t}OOH catalyzes the epoxidation of a wide range of allylic and homoallylic alcohols with high selectivities and catalytic turnovers in CO_2. We have also investigated other known catalysts such as VO(acac)$_2$ and Mo(CO)$_6$ for oxidations in dense phase CO_2. In the presence of chiral ancillary tartrate ligands, titanium isopropoxide catalysts lead to epoxides with high enantioselectivity in this medium in what is believed to be the first example of stereoselective oxidation in a supercritical fluid. We have found that the VO(OPr^i)$_3$-catalyzed epoxidation of allylic and homoallylic alcohols proceeds three times faster in CO_2 than in hexane, a solvent to which CO_2 solubility and reactivity have been compared.[3]

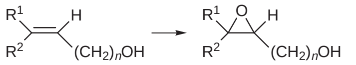
Several recent publications have demonstrated the potential of supercritical CO_2 as an alternative reaction medium for synthetic transformations.[4] Although there are several descriptions of mostly non-selective, low conversion, heterogeneous oxidations,[5] there have been no reports on selective homogeneous metal-catalyzed oxidations in dense phase carbon dioxide despite the fact that CO_2 is oxidatively stable and therefore should be an ideal solvent for this chemistry. Table 1 contains our results from a wide range of allylic and homoallylic alcohols which were oxidized with high conversions and selectivities to the corresponding epoxides using VO(OPr^i)$_3$ and Bu^{t}OOH in liquid CO_2 at 25 °C. We could find no inherent advantage of operating above the critical point of CO_2 since these reactions are often carried out at or below room temperature in conventional solvents. Therefore, the majority of our studies focused on liquid carbon dioxide. Under the anhydrous conditions of our experiments the reactions were visibly homogeneous and the product epoxides were found to be stable and could be isolated in high yields as their acetate derivatives (up to 91%).[6]

We have found that the reactivity of olefins with Bu^{t}OOH and VO(OPr^i)$_3$ as a catalyst parallels that reported in conventional solvents; activated olefins react faster than simple olefins[7] and allylic alcohols react faster than homoallylics.[8] At 25 °C most homoallylic and allylic alcohols reacted completely within 24 h with VO(OPr^i)$_3$, while no detectable reaction was observed for oct-1-ene and cyclohexene under the same reaction conditions. Allylic alcohols were found to react about four times faster than homoallylics.

We studied the kinetics of the VO(OPr^i)$_3$-catalyzed epoxidation of olefins to benchmark the reactivity in CO_2 relative to that in organic solvents since no rate data in any solvent have been reported for epoxidation reactions with this catalyst to date. The rate law was found to be first order in olefin, oxidant and catalyst with an inverse, non-integral dependence on Bu^{t}OH. Table 2 summarizes our kinetic data and shows the overall solvent effect on the epoxidation reaction is not great, as expected for such a non-polar (and non-ionic) reaction. At low constant catalyst concentrations, and during initial conditions (low [Bu^{t}OH]), we can consider the observed rate constant to be pseudo-second order. The rate constant, k', for (*Z*)-non-3-en-1-ol in CO_2 was determined to be $9\ \text{M}^{-1}\ \text{s}^{-1}$ at 25 °C. Rates for epoxidations using VO(OPr^i)$_3$ are slower than those observed in CH_2Cl_2 by a third and are roughly equal to those observed in toluene and acetonitrile. The rate constant is about three times larger in CO_2 than in hexane, suggesting that aromatic solvents may be better models than alkanes for solubility in dense phase carbon dioxide.§ The rate of the epoxidation reaction using VO(OPr^i)$_3$ was found to be at least 20-fold slower when run with 90% Bu^{t}OOH in water rather than anhydrous Bu^{t}OOH–decane.¶ VO(OPr^i)$_3$ is a moisture sensitive catalyst and is subject to hydrolysis of the V–OR bonds to form stable, and apparently CO_2-insoluble, complexes in the presence of H_2O thus limiting its activity.

VO(acac)$_2$ is an effective epoxidation catalyst in organic solvents but we have been unable to obtain significant

Table 1 Epoxidation of allylic and homoallylic alcohols with VO(OPr^i)$_3$ in liquid CO_2[a]

		*n*	Conversion %	Selectivity (%)	
R^1	R^2			Epoxide	Aldehyde
Me	H	1	> 99	85	15
Me(CH$_2$)$_2$	H	1	> 99	> 99	—
Me	Me	1	> 96	86	—
Me$_2$C=CH(CH$_2$)$_2$	Me	1	> 99	> 95	—
Me	Me$_2$C=CH(CH$_2$)$_2$	1	> 99	> 99	—
H	Et	2	> 99	89	—
Et	H	2	> 99	89	—
H	Me(CH$_2$)$_4$	2	> 99	99	—

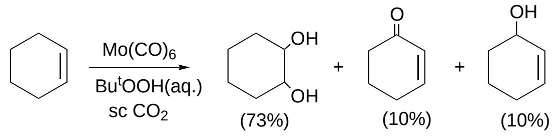
[a] 24 h reaction in liquid CO_2 (10.3 bar), 1.47 mM VO(OPr^i)$_3$ (3.5 mol%), 0.42 mM substrate, 100 mM ROOH, magnetically stirred and analyzed by GC.

Table 2 Rate of epoxidation of (*Z*)-non-3-en-1-ol with $VO(OPr^i)_3$ in serveral solvents[a]

Solvent	$k'/\text{M}^{-1}\ \text{s}^{-1}$	Relative rate
CH_2Cl_2	30	3.3
MeCN	18	2.0
PhMe	17	1.9
CO_2	9	1.0
CCl_4	5	0.6
n-C_6H_{14}	3	0.3

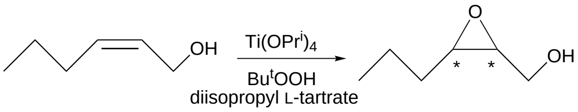
[a] $[VO(OPr^i)_3]$ = 1.47 mM (3.5 mol%), $[Bu^tOOH]$ = 100 mM, [olefin] = 42 mM, T = 24 °C, CO_2 reactions run at 29 bar. $k' = k_{\text{initial,pseudo second order}}\,[VO(OPr^i)_3]$. Rates reported in this work are accurate to within 10%.

conversions in dense phase CO_2 under similar conditions, presumably due to the limited solubility of $VO(acac)_2$ in CO_2. We are in the process of examining other, more 'CO_2-philic', acetylacetonate-based ligands including highly fluorinated systems. We have also examined the Mo(CO)–Bu^tOOH oxidation system and found that unactivated alkenes such as cyclohexene can be oxidized to their corresponding diols in CO_2 at elevated temperatures [95 °C, eqn. (1)].[9] We were surprised to find that oxidations utilizing aqueous Bu^tOOH (*e.g.* 90% Bu^tOOH–H_2O) gave significantly higher conversions than those run with dry Bu^tOOH (*e.g.* Bu^tOOH–decane) for the $Mo(CO)_6$ system suggesting an interesting effect of water.‖ High concentrations of Mo catalysts (200 mg, 12.5 mol%) were necessary for this reaction. The oxidation of cyclohexene resulted in a 73% selectivity to cyclohexene-1,2-diol at 74% conversion (presumably from the hydrolysis of cyclohexene oxide) during a 12 h reaction using aqueous Bu^tOOH with additional products derived from allylic oxidation [eqn. (1)]. Using anhydrous Bu^tOOH resulted in only 15% conversion of cyclohexene to oxidized products.



(1)

We have found that $Ti(OPr^i)_4$, in the presence of chiral tartrate ligands, results in enantioselective epoxidation catalysis in CO_2 [eqn. (2)]. Although the limited solubility of diethyl tartrate in liquid CO_2 limits the activity of this system, the use of diisopropyl tartrate in its place resulted in high conversions to epoxide. Only 16% enantiomeric excess (ee) was obtained for the epoxidation of(*E*)-hex-2-en-1-ol with the titanium–diisopropyl tartrate (0.322 mmol $Ti(OPr^i)_4$, 0.389 mmol diisopropyl tartrate) catalyst at 25 °C (93% conversion). At 0 °C the enantioselectivity increased to 87% with the same substrate during a 72 h reaction (> 99% conversion). This unoptimized result approaches the 94% ee reported by Katsuki and Sharpless.[10]



(2)

It is clear that dense phase CO_2 is an effective solvent for these olefin epoxidation reactions, with rates and selectivities similar to those observed in organic solvents. Given its oxidative stability, CO_2 shows promise as an environmentally benign solvent alternative for chemical oxidation. We are currently exploring a number of other catalytic reactions, including heterogeneous catalytic oxidation, in this important medium.**

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Notes and References

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‡ Dense phase fluids refer to systems that would be considered gases at their temperature of use, but are compressed to the point that they have liquid-like densities (ρ = 0.3 - 1.0 g cm^{-3}) including systems above their critical point (*e.g.* supercritical fluids).

§ The solubility and reactivity of dense phase CO_2 has been compared to hydrocarbons, aromatics and fluorocarbons.

¶ It is important to note that the use of decane to introduce the alkyl hydroperoxide to sc CO_2 reactions constituted less than 1% of the solvent volume (600 μl of 5.6 M Bu^tOOH in decane, or 265 μl decane in 33 ml of solvent).

‖ Preliminary results on the $Mo(CO)_6$-catalyzed oxidation of cyclic olefins with Bu^tOOH (aqueous and anhydrous in decane) yielded $k' = 5 \times 10^{-5}$ s^{-1} for anhydrous ROOH, $k' = 1{\times}10^{-3}$ s^{-1} for aqueous ROOH.

** The overall experimental setup and the general experimental procedures including sampling and product recovery have been described in detail elsewhere.[4,11] All high pressure reactions were carried out in custom-built stainless steel high pressure cells (33 ml volume) with sapphire view windows which enabled the direct visual observation of reactions. Proper safety precautions were taken for these high pressure reactions. An homogeneous solution was observable and complete conversion to the corresponding epoxide was detected, usually within 2 h. Yields were determined by gas chromatography of letdown solutions using authentic standards when available. GC–MS and ^1H NMR analysis were also used to confirm product identification.

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