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Chemoenzymatic Epoxidation of Alkenes by Dimethyl Carbonate and Hydrogen Peroxide

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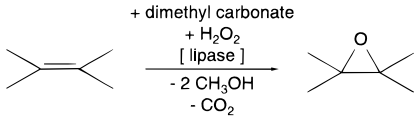
ABSTRACT



Monoperoxy carbonic acid methyl ester can be generated under neutral conditions by lipase-catalyzed perhydrolysis of dimethyl carbonate with hydrogen peroxide. It can be used in situ for the selective and efficient epoxidation of olefins; the unstable coproduct carbonic acid monomethylester decomposes to carbon dioxide and methanol. Thus, an "acid-free" Prileshajev epoxidation is realized, which is especially useful for the epoxidation of acid-sensitive substrates such as *β*-pinene.

Countless processes for the epoxidation of C=C bonds have been proposed. However, no method, including those that are transition metal catalyzed[1] or using new oxidants,[2] has been able to replace *m*-chloroperbenzoic acid as the work horse in organic synthesis, although mcpba is neither cheap nor completely harmless.

In the chemical industry, short chain peroxy acids are the oxidants of choice for all epoxidations except ethylene, propylene, and very recently butadiene. Because these short chain peracids—preferably performic and peracetic acid—are less stable than mcpba and therefore dangerous to be handled or stored in large amounts, they are usually made in situ with the help of a strong acidic catalyst (sulfuric acid, ion exchanger). Disadvantageously, the oxidant therefore must be buffered for most applications.[3] But even in this case the coproduct of the epoxidation is always an acid causing numerous consecutive reactions by epoxide ring opening. Some nonacidic oxidants for epoxidation have been described (e.g. 5-hydroperoxycarbonylphthalimide,[4] perfluorooxaziridines,[5] methyltrioxorhenium/pyridine,[6] or dioxiranes[7]), but they all suffer from various drawbacks.

Attempts have been made to use derivatives of peroxy carbonic acid as oxidants. These derivatives have been prepared from either carbonyl imidazoles[8,9] or carbodiimides,[10] which both readily react with H_2O_2, or from peroxydicarbonates[11] or chloroformic esters[12] under alkaline conditions, so that again these methods are unsuitable for most in situ oxidations.

Since Björkling et al.[13] converted middle chain fatty acids with hydrogen peroxide to peroxy acids by lipase catalysis, we used this method for the self-epoxidation of unsaturated

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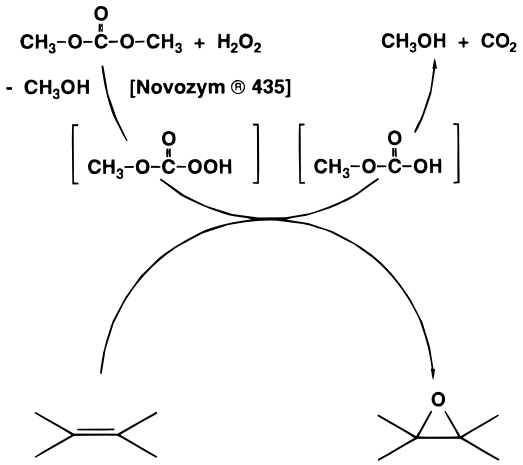
fatty acids[14] and developed lipase-catalyzed perhydrolysis of carboxylic acid esters with H_2O_2 acids for a variety of in situ epoxidations.[15] We found that in this way the scope of the reaction can be extended;[16] particularly, by perhydrolysis of ethyl acetate we generated peroxy acetic acid in situ.[17]

We now report that dialkyl carbonates can be perhydrolyzed in the same way and that alkenes present are epoxidized.[18] Novozym 435, an immobilized lipase from *Candida antarctica*, was used as the catalyst, because it has been found to be the best lipase in terms of activity/cost; furthermore, it is stable enough for multiple reuse.[11] Any short chain dialkyl carbonate may be perhydrolyzed, but dimethyl carbonate was applied for the actual epoxidations, because only dimethyl carbonate is produced industrially from the alcohol and CO without using phosgene.[19] Although we are still looking for conclusive evidence of the peroxy intermediate, we assume that monoperoxy carbonic acid monomethyl ester is the active oxidant. Fortunately, no acidic products can be found in the reaction mixture. The resulting carbonic acid monomethyl ester probably decomposes to methanol and CO_2 under the reaction conditions. Blank experiments without lipase gave no measurable amount of peroxy acid under neutral conditions. The proposed reaction mechanism is shown in Scheme 1.

Scheme 1. Epoxidation of Alkenes by Lipase-Catalyzed Perhydrolysis of Dimethyl Carbonate



In a typical epoxidation 1 mmol of the olefin was dissolved in 10 mL of dimethyl carbonate and 200 mg of Novozym 435 (supplied by Novo Nordisk Biotechnologie GmbH, Mainz, Germany) was added. Then5 mmol of H_2O_2 (60%) was added in small portions over 6 h. Afterward the mixture was stirred for another 16 h and dried over Na_2SO_4 and Na_2SO_3 to reduce the excess H_2O_2. Yields were determined by GC using an internal standard. Products were identified by comparison with authentic samples and/or by GC/MS. Larger samples for preparative workup were distilled directly after drying.

The results of the chemoenzymatic epoxidation of various alkenes with dimethyl carbonate and hydrogen peroxide are summarized in Table 1. Results of the epoxidation of the same alkenes by Novozym 435-catalyzed perhydrolysis of ethyl acetate are included for comparison. Upon epoxidation of these alkenes by Novozym 435/dimethyl carbonate/H_2O_2, yields of 67−100% were achieved with selectivities of > 98% (no byproducts were visible in GC spectra).

Table 1. Epoxidation of Alkenes by Novozym 435-Catalyzed Perhydrolysis of Dimethyl Carbonate and Ethyl Acetate

		yield of epoxide (mol %)	
		peroxy acid generated from (solvent):	
no.	alkene	dimethyl carbonate[a]	ethyl acetate[b]
1/1	1-octene	67	61−81
1/2	4-octene	92	94
1/3	1-tetradecene	69	71
1/4	7-tetradecene	100	90
1/5	styrene	78	73−92
1/6	norbornene	83	92
1/7	α-pinene	85	72
1/8	β-pinene	77	3
1/9	cyclohexene	83	64

[a] 0.1 mol/l alkene in dimethyl carbonate; C=C: H_2O_2 (60%) = 1:5; 5 mmol C=C/g Novozym 435; 16 h; 20 °C for internal C=C; 40° for terminal C=C. [b] See ref 14.

In most cases, the results of the lipase-mediated epoxidation by peroxy acetic acid and monoperoxy carbonic acid monomethyl ester are very similar. There are, however, two notable exceptions. β-Pinene (Table 1/8), well known for its acid-catalyzed rearrangements, cannot be epoxidized by perhydrolysis of ethyl acetate, but using dimethyl carbonate we achieved a good yield of 77% without any further optimization. The epoxidation of cyclohexene with Novozym 435/ethyl acetate/H_2O_2 leads to about 30% diol as the byproduct, whereas with dimethyl carbonate selectivity is again high.

In conclusion, the epoxidation by lipase-catalyzed perhydrolysis of dimethyl carbonate is an easy-to-use method especially suitable for acid-sensitive substrates. It exemplifies the usefulness of lipase-catalyzed perhydrolysis to obtain a variety of peracids as tailor-made oxidants.

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