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Ethyl Cyanoformate/Hydrogen Peroxide and Related Combination Systems, Novel Epoxidizing Systems of Olefins

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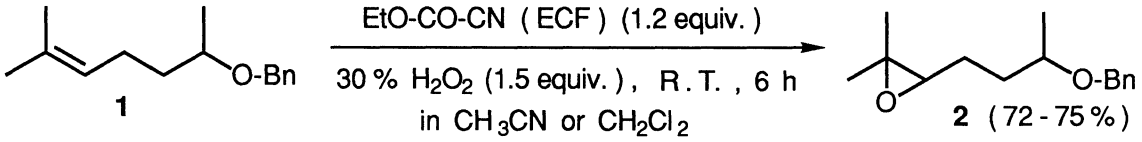
A combination system of ethyl cyanoformate and hydrogen peroxide was found to epoxidize olefins in a stereospecific manner at room temperature. Asymmetric epoxidation was observed with menthyl cyanoformate/hydrogen peroxide system.

Epoxidation of olefins with high chemo-, stereo-, and site-selectivity is one of the most important functionalizations of olefins.[1] For olefin epoxidation, m-chloroperbenzoic acid (MCPBA) is one of the most reliable and widely used reagents. In the recent commercial information from Aldrich Chemical Co., one of the major supplier, however, MCPBA is announced to be unavailable soon primarily due to hazards associated with its manufacture.[2] Since the aqueous solution of hydrogen peroxide (H_2O_2) of moderate concentrations (30-50%) is easily available and not so hazardous, the solution has been used as the terminal oxidant for epoxidation of olefins either in the presence of transition metal catalysts[3a] including hetero-poly acids[3b] and metallo-porphyrins[3c] or in combination with various formal dehydrating agents of H_2O_2[1b] such as nitriles,[4a] isocyanates,[4b] carbodiimides,[4c] benzeneseleninic acid,[4d] ethyl chloroformate,[4e] tetrachloroacetone,[4f] and diethyl phosphorocyanidate.[4g] We now disclose a new and mild reagent system, ethyl cyanoformate (ECF)/ 30% H_2O_2, which epoxidizes olefins in a stereospecific manner and report on an attempt at asymmetric epoxidation using chiral alkyl cyanoformates.

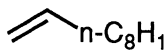
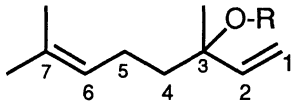
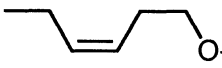
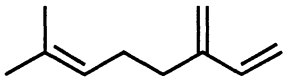
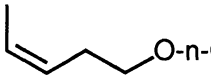
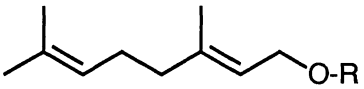
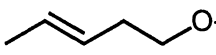
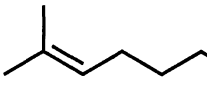
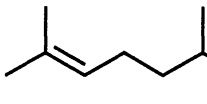
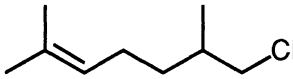
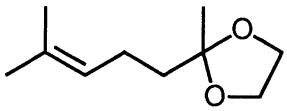
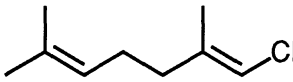
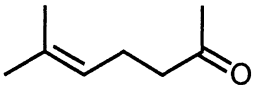
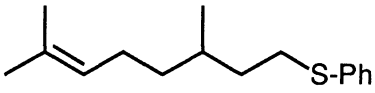
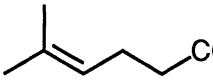
ECF has been known as the Mander's reagent and used as an easily available ethoxycarbonylating agent.[5] In a consideration of the nucleophilicity of hydroperoxide ion (^-OOH),[6] we envisaged that ECF on treatment with H_2O_2 even in the presence of water or alcohols generates an epoxidizing agent O-ethylperoxycarbonic acid (Et-O-CO-OOH), which has been known to be formed in situ by reaction of ethyl chloroformate with H_2O_2.[4e] Treatment of an olefin (**1**) with ECF (1.2 equiv.) and 30% H_2O_2 (1.5 equiv.) at room temperature for 6 h either in CH_3CN or CH_2Cl_2 gave an epoxide (**2**) as a diastereomeric mixture in 72% or 75% yield, respectively. Since olefins are not epoxidized with aqueous 30% H_2O_2 under the conditions[4a] without ECF, the epoxidation by the present system is clearly ascribed to O-ethylperoxycarbonic acid formed in situ. A variety of olefins including linear monoterpenoids with various functional and/or protecting groups were led to the corresponding epoxides by the present method and the results are summarized in Table 1.

The epoxidation by the system described proceeded in a stereospecific manner with retention of

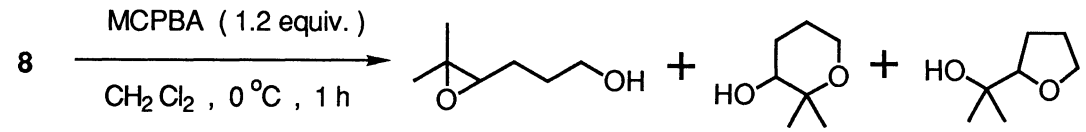


1 **2** (72 - 75 %)

Table 1 .

Run	Olefin	% Yield of epoxide	Run	Olefin	% Yield of epoxide
1		**3** 16 [a,c]	12		**14** R = H 82[a] (only 6,7 -)
2		**4** R = H 72 [a] (only cis)	13		**15** R = Ac 84[a]
3		**5** R = Bn 75 [b]	14		**16** 79[a] (only 6,7 -)
4		**6** 72 [b] (only cis)			
5		**7** 76 [b] (only trans)			6,7- 2,3- 2,3;6,7-
6		**8** R = H 89[a]	15		**17** R = H 52 37 0[a]
7		**9** R = Bn 74[a]	16		**18** R = Bn 57 0 2[a]
			17		**19** R = CH_2O-  -OMe 67 3 9[a]
8		**10** 82[a]	18		**20** 46[b,d]
9		**11** 68[a]	19		**21** 66[b] (only 6,7 -)
10		**12** 87[b]			
11		**13** 60[a]	20		**22** 75 (sulfoxide)[a]

a) Reaction was carried out in CH_3CN . b) Reaction was carried out in CH_2Cl_2.
c) 80 % of the starting material was recovered . d) Product was 6,7 - epoxy - cyanohydrin .



8 **23** (7 %) **24** (34%) **25** (35 %)

the configuration of olefins applied (runs 2-5). Tri-substituted olefins underwent epoxidation more rapidly than terminal olefins (runs 12, 13) and a 1,3-diene system (run 14), and the tendency followed the general behavior of the substitution patterns of olefins in epoxidation with peroxycarboxylic acids.[7] The method is applicable to olefins with alcohol function (runs 3, 6, 12, and 15). Geraniol (**17**) afforded a mixture of position-isomeric (2,3)- and (6,7)-epoxides, and O-protected geraniols (**18** and **19**) produced mixtures of 6,7-epoxides and 2,3;6,7-di-epoxides, respectively. The fact that an epoxy-cyanohydrin was obtained from citronellal (**20**), an olefin with aldehyde group, indicated in situ generation of hydrogen cyanide (HCN).[8] No Baeyer-Villiger oxidation was observed in the oxidation of 6-methyl-5-hepten-2-one (**12**), which afforded the desired epoxy-ketone in a high yield. Sulfur oxidation of an olefin (**22**) containing phenylthio group took place in preference to epoxidation to furnish the corresponding sulfoxide under the conditions (run 20).

It should be worth noting that the epoxidizing system described here presents nearly neutral conditions and generates the active oxidant O-ethylperoxycarbonic acid, which releases ethanol, carbon dioxide, and a very weak acid HCN (pKa=9.3) after epoxidation. In contrast, MCPBA generates m-chlorobenzoic acid (pKa=3.8), and reaction of ethyl chloroformate and H_2O_2, another method for generation of O-ethylperoxycarbonic acid, produces a strong acid hydrogen chloride (HCl). The acidity of the oxidation media influenced the course of the reaction of a certain hydroxy olefin. Thus, treatment of 5-methyl-4-hexen-1-ol (**8**) with MCPBA at 0 °C afforded the desired epoxide (**23**) in a minor proportion along with the cyclized products (**24** and **25**) in a 1:5:5 ratio, although the desired epoxide (**23**) was obtained in 89% yield by the present system (run 6):

Alkyl cyanoformates are known to be prepared from carbonyl cyanide ($(NC)_2CO$) and alcohols.[9] Since several chiral secondary alcohols are easily available, we attempted to make and utilize chiral alkyl cyanoformates for asymmetric epoxidation.[1b,c,10] Thus, three chiral alkyl cyanoformates (**29**, **30**, and **31**) were prepared from (S)-1-phenyl-ethanol, (S)-2-octanol, and (-)-menthol, respectively, according to the reported method,[9] and epoxidation of 4-methyl-1-phenyl-3-pentene (**26**) was carried out by using the chiral cyanoformates. Epoxide (**27**) obtained was converted by the known method[11] using $Al(O\text{-}i\text{-}Pr)_3$ to the corresponding allylic alkohol (**28**), the enantiomeric excess (% ee) of which was determined by HPLC using a column with chiral

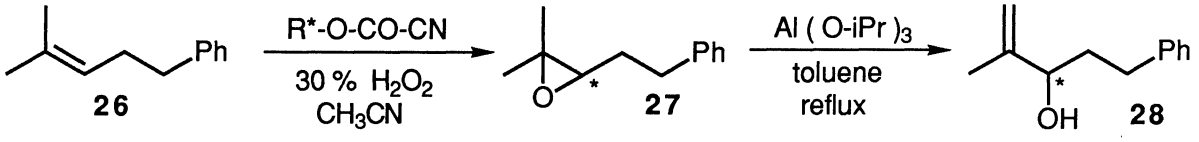
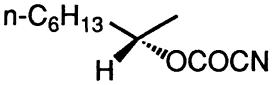
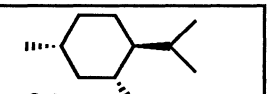


Table 2.

R*-O-CO-CN	 **29**	 **30**	 **31**
Chemical yield / % of **27**	69	74	76
% ee of **27**	3	13	20

stationary phase (SUMIPAX-OA-4000) after derivatization to the corresponding 3,5-dinitrophenylurethane. The results are summarized in Table 2. Among the cases tried, the highest chiral induction (20% ee) was observed in the epoxidation using (-)-menthyl canoformate (**31**). The epoxidation described here seems promising for asymmetric epoxidation of unfunctionalized olefins, though the results obtained in three examples was less satisfactory. The design of more effective chiral alkyl cyanoformate/H_2O_2 systems is one of our goals.

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