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Kinetic Resolution of Chiral Hydroperoxides *via* Sharpless Epoxidation

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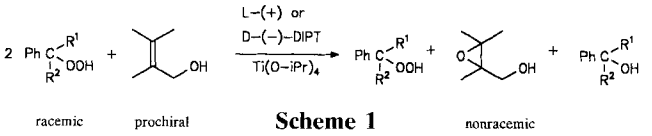
Abstract. The kinetic resolution of tertiary hydroperoxides *via* catalytic Sharpless epoxidation with various allylic alcohols has been investigated. By using 1-cyclohexyl-1-phenylethyl hydroperoxide an enantiomeric excess (e.e.) of up to 29 % of the resolved hydroperoxide has been observed at a consumption of the racemic hydroperoxide of nearly 50 %. The e.e. can be increased, however, only by raising the hydroperoxide consumption.

Optically active hydroperoxides which may be used as potential stereoselective oxidizing reagents are of great interest. First attempts to obtain homochiral hydroperoxides by the oxidation of optically active alcohols or their derivatives with hydrogen peroxide showed that this oxidation proceeds with inversion accompanied by a high degree of racemization [1]. Some optically active hydroperoxides in which the hydroperoxy group is attached directly to an asymmetric C-atom were obtained by photooxidation of thiazolidines [2], oxidation of 2,3-unsaturated glycosides with hydrogen peroxide [3] or by enzymatic oxidations [4] and multistep syntheses from derivatives of polyunsaturated carboxylic acids [5].

The resolution of simple hydroperoxides as 1-phenylethyl hydroperoxide was successfully accomplished in liquid chromatography of diastereomeric derivatives [6] or by enzymatic acylation in the presence of lipases [7], by the oxidation of sulfides in the presence of chloroperoxidase [8], or quite recently by horseradish peroxidase-catalyzed enantioselective reduction in the presence of guaiacol [9].

Results and Discussion

In a preliminary communication [10] we showed that in the case of 1-methyl-1-phenylpropyl hydroperoxide (**1**) the Sharpless epoxidation represents a possibility for the kinetic resolution. The reaction between the racemic hydroperoxide and the prochiral allylic alcohol yields a homochiral epoxyalcohol, an enriched hydroperoxide enantiomer and an enriched alcohol enantiomer with the opposite rotation compared to the hydroperoxide. That means that besides a kinetic resolution of the chiral hydroperoxide there proceeds an enantioselective epoxidation and so three nonracemic compounds are generated simultaneously (see Scheme 1).

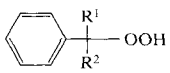


Scheme 1

We extended this investigation to other hydroperoxides and numerous allylic alcohols in order to point out the influence of the structure of components on the degree of resolution. The hydroperoxides used have been prepared by alkylation of hydrogen peroxide with alcohols in acidic media. They are summarized in Table 1. All hydroperoxides prepared have been characterized by ^{13}C NMR-spectra. Compared to the corresponding alcohols the chemical shift of the hydroperoxides obtained corresponds with the general data and rules published by Olah et al. [12] and Kropf et al. [13] (see Experimental).

The kinetic resolution of the hydroperoxides **1–5** has been investigated in the Sharpless epoxidation according to Scheme 1. The enantiomeric excess (e.e.) ob-

Table 1 *tert*-Alkyl Hydroperoxides



	R^1	R^2	method[a]	yield (%)	b.p. (°C)/ torr
1	CH_3	C_2H_5	A	72	61–63/0.06[b]
2	CH_3	n-C_3H_7	A	46	69–70/0.05
3	CH_3	i-C_3H_7	A	25	60/0.1
4	CH_3	cyclohexyl	B	67	m.p. 73
5	C_2H_5	n-C_3H_7	A	32	80/0.07

[a] method A: in the presence of catalytic amount of concentrated H_2SO_4; method B: in H_3PO_4
[b] Reference [11]: b.p. 80 °C/0.1torr

served on the resolution of **1**, **2** and **4** after the conversion of nearly 50 % of the hydroperoxide at −20 °C and determined by HPLC [14] is shown in Table 2. In the case of **3** and **5** practically no e.e. could be observed. The best results were obtained using phenyl-substituted allylic alcohols, whereas in the case of allyl alcohol and its methyl derivatives the e.e. is very low. Upon resolution of **4** with (E)-α-phenyl cinnamyl alcohol an e.e. of up to 29 % was reached.

As already shown in our short communication, in the case of **1** the solutions after resolution according to Scheme 1 contain the corresponding alcohol in which the enantiomer with the opposite rotation in comparison to the hydroperoxide is enriched. This observation has been made using any allylic alcohol and hydroperoxide. In some cases the e.e.'s of the epoxyalcohols formed were determined by HPLC. As expected, the results obtained amounted to >90 %.

In addition to the allylic alcohols shown in Table 2 also geraniol, nerol, crotyl alcohol and 4-benzyloxy-2-buten-1-ol were used for the resolution of **1**, but only a very low e.e. (5–8 %) was observed. Even the use of an allylic alcohol with a bulky group, such as 2-adamantylidenethan-1-ol, did not give better but rather lower e.e.. So the influence of the allylic alcohol structure on the degree of resolution seems to be more complex than expected.

Of course, the enantiomeric excess depends on the conversion of the racemic hydroperoxide. This dependence was investigated for the most favourable combination of (E)-α-phenyl cinnamyl alcohol and **4**.

Figure 1 shows that the experimentally determined values correspond with a computer generated curve of the stereoselectivity factor [15] E = 2.73. This low value

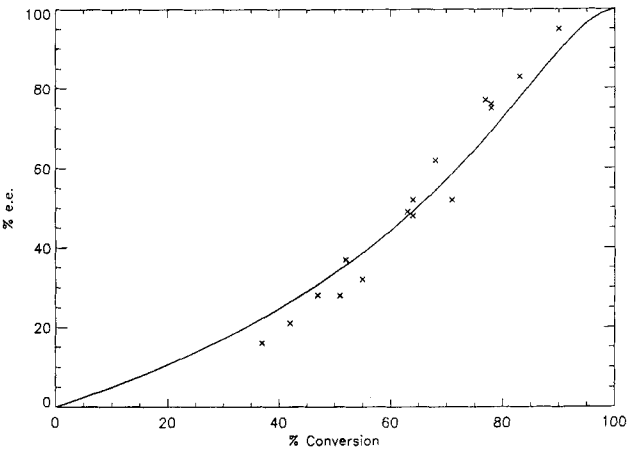


Fig. 1 Kinetic resolution of **4** at −20 °C using (E)-α-phenyl-cinnamyl alcohol: Dependence of % e.e. on conversion.

The curve for E = 2.73 was computer-generated from the equation

$$E = \frac{\ln(1 - C)(1 - ee)}{\ln(1 - C)(1 + ee)}$$

were E is the stereoselectivity factor and C is the conversion. x = experimentally determined values

Table 2 Kinetic Resolution of *tert*-Alkyl Hydroperoxides[a]

allylic alcohol	DIPT[b]	1-Methyl-1-phenyl-propyl hydroperoxide **1**			1-Methyl-1-phenyl-butyl hydroperoxide **2**			1-Cyclohexyl-1-phenyl-ethyl hydroperoxide **4**		
		(+) %	(−) %	e.e. %[c]	(+) %	(−) %	e.e. %	(+) %	(−) %	e.e. %
allyl alcohol	L-(+)	51.5	48.5	3.0	51.4	48.6	2.8	50.6	49.4	1.2
	D-(−)	48.4	51.5	3.2	47.8	52.2	4.4	48.8	51.2	2.4
3-methyl-2-butenol	L-(+)	52.1	47.9	4.2	51.8	48.2	3.6	54.2	45.8	2.4
	D-(−)	48.2	51.8	3.6	48.4	51.6	3.2	46.0	54.0	8.0
(*Z*)-2-hexen-1-ol	L-(+)	57.3	42.7	14.6	52.0	48.0	4.0	53.7	46.3	7.4
	D-(−)	43.5	56.5	13.0	47.4	52.6	5.2	46.6	53.4	6.8
(*Z*)-cinnamyl alcohol	L-(+)	50.8	49.2	1.6	52.4	47.6	4.8	56.7	43.3	13.4
	D-(−)	49.1	50.9	1.8	48.0	52.0	4.0	45.6	54.4	8.8
(*E*)-2-hexen-1-ol	L-(+)	46.9	53.1	6.2	47.0	53.0	6.0	52.9	47.1	5.8
	D-(−)	53.2	46.8	6.4	51.5	48.5	3.0	49.2	50.8	1.6
(*E*)-cinnamyl alcohol	L-(+)	44.3	55.7	11.4	45.5	54.5	9.0	47.6	52.4	4.8
	D-(−)	56.9	43.1	13.8	55.0	45.0	10.0	52.6	47.4	5.2
(*E*)-α-phenyl-cinnamyl alcohol	L-(+)	41.8	58.2	16.4	43.0	57.0	14.0	35.6	64.4	28.8
	D-(−)	57.4	42.6	14.8	55.0	45.0	10.0	64.5	35.5	29.0
β-phenylcinnamyl alcohol	L-(+)	41.4	58.6	17.2				40.8	59.2	18.4
	D-(−)	60.3	39.7	20.6				58.0	42.0	16.0
2-phenylallyl alcohol	L-(+)	56.7	43.3	13.4						
	D-(−)	44.9	55.1	10.2						
2-methyl-3-phenyl-2-propen-1-ol	L-(+)	46.2	53.8	7.6				45.2	54.8	9.6
	D-(−)	53.2	46.8	6.4				57.4	42.6	14.8

[a] After consumption of nearly half the amount of starting hydroperoxide; [b] DIPT = diisopropyl tartrate; [c] margin of error ±1 %

expressing the small difference of the reaction rate of the hydroperoxide enantiomers in the resolution reaction limits the use of this reaction for preparative purposes.

The influence of the temperature on the e.e. was investigated in the range from 0 °C to −60 °C. As expected, the reaction rate increased with rising temperature. At 0 °C the conversion of **5** already amounted to 75 % after 15 min. and the e.e. observed was 50 %, whereas at −60 °C the conversion was 30 % after 1 hour and the e.e. determined was 40 %. Comparing these data with the results at −20 °C in Figure 1 it becomes obvious, that the e.e. increases significantly with decreasing temperature.

The change of the molar ratio of allylic alcohol : hydroperoxide from 1 : 2 to 1 : 1 and toward a higher excess of allylic alcohol as well as the increase of the amount of $Ti(OiPr)_4$ and DIPT lead to a higher reaction rate, but it has no clear influence on the e.e..

Surprisingly, the allylic alcohols used can be arranged in two groups according to the rotation of the resulting enriched hydroperoxide enantiomer. Using (Z)-allylic alcohols in the presence of L-(+)-diisopropyl tartrate (DIPT) an excess of (+)-hydroperoxide was found in the solution, whereas (E)-allylic alcohols in the presence of the same DIPT afforded the enriched (−)-hydroperoxide enantiomer except for **4**. Therefore, we conclude that the diastereoisomerism of the starting allylic alcohols has a predominance in directing the stereochemistry of the reaction.

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Experimental

^{13}C NMR spectra were measured on a Varian Gemini 300 spectrometer in $CDCl_3$ (internal standard: HMDS)

Allylic alcohols

Most of the allylic alcohols are commerically available.
(Z)-Cinnamyl alcohol was prepared from phenylacetylene by hydroxymethylation followed by Lindlar reduction [16]. *α-Phenylcinnamyl alcohol* was obtained by reduction of α-phenylcinnamic acid with $LiAlH_4$ [17], *β-Phenylcinnamyl alcohol* by reduction of β-phenylcinnamaldehyde with $NaBH_4$ [18], *2-adamantylideneethan-1-ol* by reduction of adamantylideneacetic acid with $LiAlH_4$ according to [19]. *2-Phenylallyl alcohol* was prepared by treatment of propargyl alcohol with phenylmagnesium bromide [20].

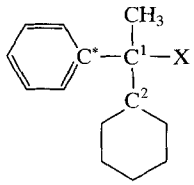
Hydroperoxides (1–5)

The hydroperoxides used as starting compounds were prepared by reaction of the corresponding alcohols with 30 – 70 % hydrogen peroxide either in the presence of a catalytic amount of sulfuric acid (method A) [11] or in phosphoric acid (method B) [21]. As an example the preparation of **4** is described below.

1-Cyclohexyl-1-phenylethyl hydroperoxide (**4**)

A mixture of 8.45 g (0.04 mol) 1-cyclohexyl-1-phenylethanol [22], 40 ml of 85 % phosphoric acid and 40 ml of 50 % hydrogen peroxide was vigorously stirred for 5 hours at 50 °C. The organic layer was separated and the aqueous part was extracted three times with petroleum ether after dilution with 50 ml water. The extract was combined with the organic layer and dried after washing with water and then several times with saturated $NaHCO_3$-solution. After partial evaporation of the solvent, the hydroperoxide crystallized in colourless needles.
Yield: 5.88 g (67 %); m.p. 73 °C; peroxidic oxygen: 100 %
$C_{14}H_{20}O_2$ calcd.: C 76.33 H 9.15
(220.31) found: C 76.09 H 9.18
^{13}C NMR chemical shift see Table 3

Table 3 ^{13}C NMR Chemical Shifts of **4**[a]



	X=OOH	X = OH	Δ[b]
C^1	88.89	76.55	12.34
CH_3	18.34	29.37	−11.03
C^2	47.57	48.98	−1.41
C*-Ar	143.52	147.84	−4.32

[a] In ppm; $CDCl_3$ solvent; internal HMDS
[b] Differences in the chemical shifts of hydroperoxides and corresponding alcohols: (− = highfield shift)

All hydroperoxides were characterized by iodometric titration and ^{13}C NMR spectra; yields and boiling points (melting points) are given in Table 1.

The ^{13}C NMR spectra of hydroperoxides prepared for the first time were compared with those of the corresponding alcohols. The chemical shifts of **1–5** correspond well with data of other hydroperoxides and confirm the rules regarding the difference (Δ) of the chemical shift of the alcohols and the hydroperoxides [12, 13]. The data of the other hydroperoxides are available from the authors.

Kinetic resolutions (General procedure)

To a suspension of 250 mg of molecular sieves A3 and 10 ml of methylene chloride, which was cooled to −20 °C, 0.15 ml (0.51 mmol) of titanium(IV) isopropoxide, 0.14 ml (0.67 mmol) of L-(+)- or D-(−)-diisopropyl tartrate, 4 mmol of the hydroperoxide and 2 mmol of allylic alcohol were added. The mixture was stirred at −20 °C and the conversion of the hydroperoxide was checked by iodometric titration. After half of

the starting hydroperoxide had been consumed, 1 ml of aqueous Na_2SO_4-solution was added, the stirring was continued for 2 hours, and the temperature was allowed to rise to room temperature. The mixture was centrifugated and the liquid phase was dried with anhydrous Na_2SO_4. The hydroperoxides were separated by preparative HPLC on a column of Kieselgel 60 (Merck) with hexane/2-propanol (99.5:0.5 v/v) which was carefully dried over molecular sieves A3. The separated solutions were evaporated and the residue was used for the separation of enantiomers.

Separation of the enantiomers [14]

A chiral column (150 × 4 mm) with cellulose tris(3,5-dimethylphenyl carbamate) was used with a water-saturated mixture of hexane/2-propanol (98:2 v/v) or hexane/ethanol (9:1, v/v) as eluent. A representative example of the separation of the enantiomers of **4** is shown in Figure 2.

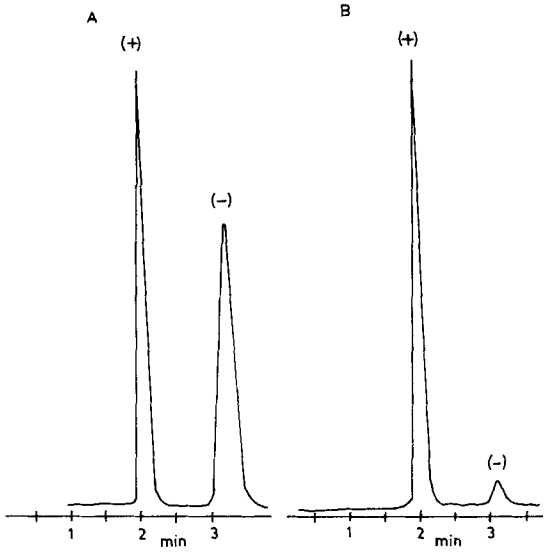


Fig. 2 Separation of the enantiomers of 1-cyclohexyl-1-phenylethyl hydroperoxide (**4**) by HPLC. Column: cellulose tris(3,5-dimethylphenyl carbamate) 150 × 4 mm, eluent: hexane/ethanol (9:1, v/v), flowrate: 1 ml/min.. A racemate; B 83 % e.e.

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