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The titanium-catalyzed, asymmetric epoxidation of allylic alcohols with optically active hydroperoxides in the presence of achiral diol ligands

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Abstract: The titanium-catalyzed, asymmetric epoxidation of dialkyl- and phenyl-substituted allylic alcohols with various enantiomerically pure hydroperoxides has been examined in the presence of achiral diol ligands. Enantioselectivities with ee values up to 50% were achieved in the oxygen transfer from (−)-(*S*)-1-phenylethyl **1a** and (−)-(*S*)-1-phenylpropyl **1b** hydroperoxides to 3-methyl-2-buten-1-ol **2a** and geraniol **2b** in the presence of the diethyl 2-hydroxy-2-hydroxymethylmalonate (DHHM) as an achiral multidentate diol ligand. The DHHM additive was ineffective in the asymmetric epoxidation of the phenyl-substituted allylic alcohols **3c–f**, and only low ee values (up to 15%) were obtained. The optically active hydroperoxides (−)-(*S*)-**1c** and (−)-**1d** gave only moderate enantioselectivities (ee values up to 24%) with or without the achiral malonate additive DHHM. The concept of titanium-catalyzed, asymmetric epoxidation with optically active hydroperoxides as oxygen donors in the presence of multidentate diols as achiral ligands is less effective in its enantioselectivity than the Sharpless *modus operandi* of employing *t*-butyl hydroperoxide as achiral oxygen donor and the C_2-symmetric tartrate as chiral auxiliary. © 1997 Elsevier Science Ltd

Introduction

The asymmetric oxidation of unfunctionalized as well as functionalized olefins is the subject of current interest and intensive research in organic synthesis.[1] For allylic alcohols, the most efficient reaction for the catalytic, enantioselective epoxidation is the Sharpless epoxidation.[1,2] Herein the oxygen donor is the achiral *t*-butyl hydroperoxide, the asymmetric induction results from catalytic amounts of optically active tartrate as chiral auxiliary.[2,3] If optically active hydroperoxides are used in epoxidations, the hydroperoxide not only serves as the oxygen-transfer reagent but also as the source of chirality without the need of tartrate as chiral auxiliary. First attempts on allylic alcohols afforded under titanium catalysis low to moderate (less than 20%) enantiomeric excesses.[4] Higher enantioselectivities (up to ee 50%) were obtained with sugar-derived hydroperoxides.[4]

Previously[5] we reported on the enzymatic kinetic resolution of chiral secondary hydroperoxides with horseradish peroxidase. In that way, the enantiomerically pure (−)-(*S*)-1-phenylethyl **1a**, (−)-(*S*)-1-phenylpropyl **1b** and (−)-(*S*)-1-indanyl hydroperoxides **1c** and ethyl (−)-5-(1-hydroperoxyethyl)-2-methylfuran-3-carboxylate **1d** were prepared and are on hand to be employed for the asymmetric epoxidation of allylic alcohols under titanium(IV) catalysis. For high enantioselectivity,[2b] a highly ordered, rigid transition state with restricted degrees of freedom is required. This is achieved in the Sharpless epoxidation by chelation of the tartrate ligand as chiral auxiliary and the activation of the achiral *t*-butyl hydroperoxide in the titanium template in form of the loaded complex **A** in Figure 1. Since in our concept, the optically active hydroperoxide was to provide the chiral environment as the oxygen donor, but additional coordination sites were thought to be essential to limit the degrees of freedom during the assembly of the loaded titanium complex, achiral diol ligands were chosen as

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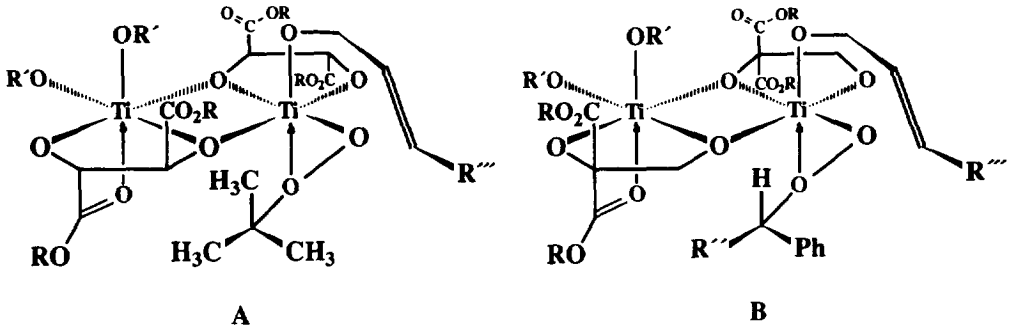
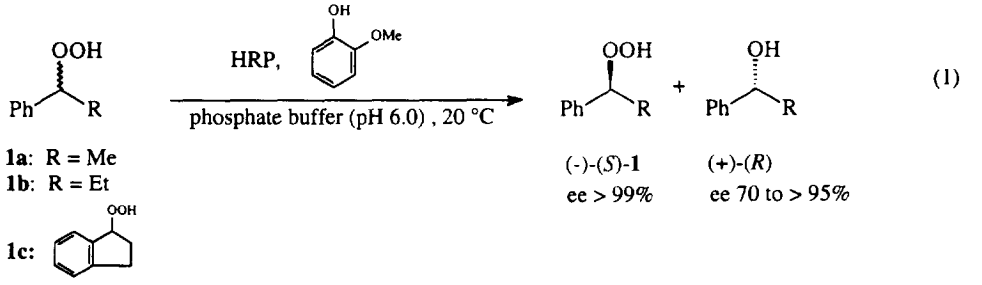


Figure 1. Postulated loaded complex in the Sharpless reaction[2b,c] (**A**) and in the asymmetric epoxidation with optically active hydroperoxides in the presence of an achiral additive (**B**).

additives. Such multidentate diol additives should help to simulate a Sharpless-like transition state (loaded complex **B** in Figure 1) to promote higher enantioselectivity in the oxygen transfer. Herein we report our efforts along these lines, in which we have examined a variety of prochiral allylic alcohols as oxygen acceptors, optically active hydroperoxides as oxygen donors, and achiral additives as multidentate ligands. Our results reveal that the loaded complex **B** is not nearly as effective in the enantioselective control as the genuine Sharpless complex **A** (Figure 1).

Results and discussion

By means of enzymatic kinetic resolution with horseradish peroxidase (HRP),[5] the optically active hydroperoxides (−)-(*S*)-**1a–c** were prepared in gram quantities with ee >99% (Eq. 1).

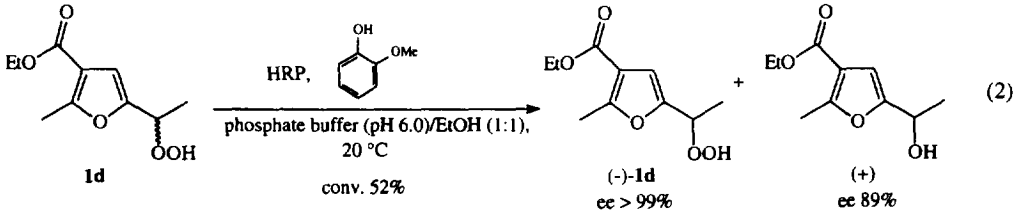


(1)

1a: R = Me
1b: R = Et
1c:

(-)-(*S*)-**1** ee > 99%
(+)-(*R*) ee 70 to > 95%

In the same way, ethyl 5-(1-hydroperoxyethyl)-2-methylfuran-3-carboxylate **1d** was enzymatically resolved for the first time to afford the enantiomerically pure (−)-**1d** (Eq. 2).



(2)

1d

conv. 52%

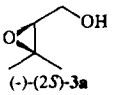
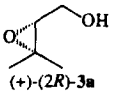
(-)-**1d** ee > 99%

(+) ee 89%

Since in the HRP-catalyzed kinetic resolution the (*S*) enantiomer is obtained for the hydroperoxides **1a–c**, it is likely that the (−)-isomer **1d** is also (*S*)-configured. Unfortunately, it has not been possible so far to assign its configuration through chemical correlation or X-ray crystallography.

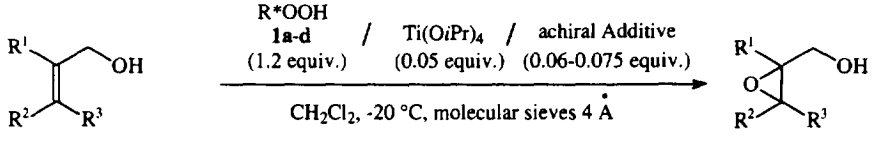
The Ti-catalyzed epoxidations were conducted in the presence of multidentate diol additives as chelating ligands (Eq. 3), for which 3-methyl-2-buten-1-ol **2a** was chosen as prochiral substrate and the

Table 1. Asymmetric epoxidation of 3-methyl-2-butenol **2a** in the presence of achiral diol additives by optically active hydroperoxides **1a–c**.

				 (-)-(2*S*)-**3a**	or	 (+)-(2*R*)-**3a**
entry	hydroperoxide	additive	t [h]	yield[a] [%]	ee[b] [%]	config.
1		-	5.0	71	27	(-)-(2*S*)
2		ethylene glycol	8.0	86	32	(-)-(2*S*)
3	(-)-(*S*)-**1a**	pinacol	5.0	96	26	(-)-(2*S*)
4		*meso*-DET	5.0	81	29	(-)-(2*S*)
5		DHHM	5.0	96	49	(-)-(2*S*)
6		-	4.5	75	30	(-)-(2*S*)
7	(-)-(*S*)-**1b**	ethylene glycol	4.5	74	32	(-)-(2*S*)
8		pinacol	5.0	71	27	(-)-(2*S*)
9		DHHM	5.0	76	45	(-)-(2*S*)
10	(-)-(*S*)-**1c**	-	5.0	72	14	(+)-(2*R*)
11		DHHM	5.0	74	13	(-)-(2*S*)
12	(-)-**1d**	-	8.5	63[c]	10	(-)-(2*S*)
13		DHHM	8.0	97[c]	21	(-)-(2*S*)

[a] Yield of isolated product after silica-gel chromatography; [b] determined by MDGC on a chiral column [hexakis (2,3,6-tri-(methyl)-β-cyclodextrin in DB 1701]; error ± 2% of the stated value; [c] conversion determined by ^{1}H NMR analysis on the crud reaction mixture; error ± 3% of the stated value; product was not isolated.

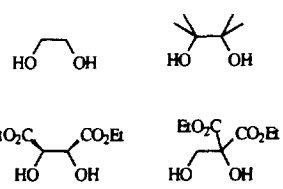
optically active (−)-(*S*)-1-phenylethyl **1a** and (−)-(*S*)-1-phenylpropyl **1b** hydroperoxides as oxygen-atom sources (Table 1).



2a-g **3a-g** (3)

2a: R^1 = H, R^2 = R^3 = Me
2b: R^1 = H, R^2 =  , R^3 = Me
2c: R^1 = R^3 = H, R^2 = Ph
2d: R^1 = R^2 = H, R^3 = Ph
2e: R^1 = Me, R^2 = Ph, R^3 = H
2f: R^1 = R^2 = Ph, R^3 = H
2g: R^1 = H, R^2 = Ph, R^3 = Me

additives



***meso*-DET** **DHHM**

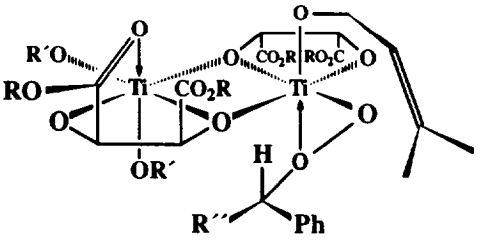


Figure 2. Postulated loaded complex of the asymmetric epoxidation of 3-methyl-2-buten-1-ol **2a** in the presence of *meso*-DET as additive with optically active hydroperoxides **1** as oxygen donor.

In the presence of ethylene glycol (entry 2) as the simplest achiral diol ligand for the epoxidation of 3-methyl-2-buten-1-ol **2a** by (−)-(*S*)-1-phenylethyl hydroperoxide **1a**, the enantiomeric excess (ee 32%) was only slightly higher than without this additive (ee 27%, entry 1). The use of the sterically more demanding pinacol (entry 3) also did not improve the enantioselectivity of the oxygen transfer.

In the Sharpless loaded complex (Figure 1, complex **A**), the bridging carbonyl groups of the tartrate have been suggested[3] to play an important role for the rigidity and the activity of the catalyst through reversible ligation; thus, in analogy, the diethyl *meso*-tartrate (*meso*-DET) was chosen (entry 5) as achiral additive to serve this purpose. Unfortunately, it had no influence on the enantioselectivity of the reaction since the ee value 29% was the same as without additive (entry 1). This failure may be explained with the help of the postulated loaded complex for *meso*-DET (Figure 2). Since in *meso*-DET both ester groups point in the same direction, for steric reasons they should be arranged opposite to the bound allylic alcohol in the titanium template.

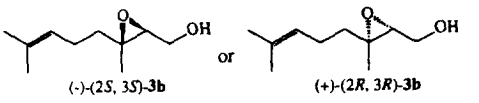
Therefore, contrary to the Sharpless transition state (Figure 1, complex **A**), the ester groups of the achiral *meso*-DET ligand in the complex of Figure 2 should not have any appreciable directing effect on the preferred enantiofacial arrangement of the allylic alcohol with respect to the O–O bond of the chiral hydroperoxide oxygen donor; thus, no additional asymmetric induction is exercised by this additive.

To circumvent this short-coming, as a new achiral additive the diethyl 2-hydroxy-2-hydroxymethylmalonate (DHHM) was chosen, in which the two ester groups are bound at the same carbon atom to preserve the desired achiral character. As shown in the postulated new transition structure (Figure 1, complex **B**), the allylic alcohol should now be forced to point away from the sterically demanding ester group towards the unsubstituted site of the diol moiety of this achiral additive. Indeed, in the asymmetric epoxidation of 3-methyl-2-buten-1-ol **2a** with (−)-(*S*)-**1a**, the ee value could be more than doubled from 22 to 49% (Table 1, entry 5).

A comparison of the enantiomeric excesses in Table 1 reveals that the increase of the sterical demand from (−)-(*S*)-1-phenylethyl **1a** to (−)-(*S*)-1-phenylpropyl **1b** hydroperoxide is too small to exercise effective enantioselective control in the epoxidation (compare entries 1–5 with entries 6–9). In both cases, the (−)-(*S*)-epoxide **3a** is formed preferentially with similar ee values, which are highest (almost 50% ee) for the malonate DHHM additive.

When the more rigid [compared to the hydroperoxides (−)-(*S*)-**1a,b** derivatives] (−)-(*S*)-1-indanyl hydroperoxide **1c** is used (entries 10 and 11), the influence of the hydroperoxide structure on the enantioselectivity becomes evident. In the reaction without additives (entry 10), the configuration of the preferred epoxide **3a** is inverted since now the (+)-(*R*) enantiomer **3a** is formed as the main isomer, but in a significantly reduced enantiomeric excess (ee 14%) compared to (−)-(*S*)-**1a,b** (ee ca. 30%). In the presence of the DHHM diol as additive (entry 11), again the (−)-(*S*)-epoxide **3a** predominates, but with a low ee value (13%). These unusual data imply that the sense in the asymmetric induction exerted by the (−)-(*S*)-**1c** hydroperoxide is counteracted by that of the achiral malonate additive and the net result is a poor enantioselectivity.

Table 2. Asymmetric epoxidation of geraniol **2b** in the presence of the achiral malonate additive DHHM and the optically active hydroperoxides (−)-(*S*)-**1a–c** as oxygen donors.



(-)-(2*S*, 3*S*)-**3b** (+)-(2*R*, 3*R*)-**3b**

entry	hydroperoxide	additive	t [h]	yield [%]	ee[b] [%]	config.
1	(-)-(*S*)-**1a**	-	4	83	25	(-)-(2*S*, 3*S*)
2		DHHM	4	91	43	(-)-(2*S*, 3*S*)
3	(-)-(*S*)-**1b**	-	4	56	20	(-)-(2*S*, 3*S*)
4		DHHM	4	83	50	(-)-(2*S*, 3*S*)
5	(-)-(*S*)-**1c**	-	8	80	6	(+)-(2*R*, 3*R*)
6		DHHM	8	64	10	(-)-(2*S*, 3*S*)

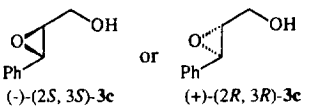
[a] Yield of isolated product after silica-gel chromatography; [b] determined by MDGC on a chiral column [hexakis (2,3,6-tri-O-methyl)-β-cyclodextrin in DB 1701]; error ± 2% of the stated value.

To examine the influence of the substrate structure on the enantioselectivity of the reaction, differently substituted allylic alcohols were epoxidized by the chiral hydroperoxides (−)-(*S*)-**1a–c** in the presence of DHHM. The same trend (Table 2) as in the epoxidation of 3-methyl-2-buten-1-ol **2a** was observed for geraniol **2b**. The use of the hydroperoxides (−)-(*S*)-**1a,b** (Table 2, entries 1–4) generally led to the (−)-(2*S*,3*S*)-epoxide **3b** as the main enantiomer in comparable enantiomeric excesses. Again, by adding DHHM, the ee value could be raised from 25% (entry 1) and 20% (entry 3) to 43% (entry 2) and 50% (entry 4). With (−)-(*S*)-1-indanyl hydroperoxide **1c** as the oxygen donor, similar results were obtained as for the epoxidation of 3-methyl-2-buten-1-ol **2a**. Compared to the epoxidation of 3-methyl-2-buten-1-ol **2a**, the longer alkyl chain in geraniol **2b** had no effect on the enantioselectivity of the oxygen transfer (Table 1).

The results for a phenyl-substituted allylic alcohol, namely the cinnamyl alcohol **2c**, are summarized in Table 3. Surprisingly, in contrast to the epoxidation of alkyl-substituted 3-methyl-2-buten-1-ol **2a** and geraniol **2b** (Tables 1 and 2), the cinnamyl alcohol **2c** led with (−)-(*S*)-**1a,b** (entries 1–5) to the (+)-(2*R*,3*R*)-epoxide **3c** as the preferred enantiomer. Thus, for this case the oxygen transfer takes place at the opposite enantio-face of the allylic alcohol, but in low enantiomeric excess (ee up to 15%). Even the formerly sucessful malonate DHHM as additive (Table 3, entries 3, 5, and 7) was ineffective in terms of the enantioselectivity. With the (−)-(*S*)-**1c** hydroperoxide, again the opposite enantiomer (−)-(2*S*, 3*S*)-**3c** was selected in the epoxidation without additive (entry 8), and the malonate additive DHHM (entry 9) had no effect.

Also, the corresponding (*Z*)-isomer, namely (*Z*)-3-phenyl-2-propen-1-ol **2d**, gave poor enantioselectivities in the asymmetric epoxidation under these conditions (Table 4). Additionally, the epoxidation of **2d** was quite sluggish, as is known for the Sharpless epoxidation of (*Z*)-configurated allylic alcohols,[2b] since reaction times of more than two days were necessary even for ca. 50% conversion. The enantiomeric excesses were in all cases low (ee up to 14%). Compared to the oxidations without additive (Table 4, entries 1, 3 and 5) which were totally unselective, the ee values could be increased for all three hydroperoxides (−)-(*S*)-**1a–c** by about 10% with the help of the malonate additive DHHM (entries 2, 4 and 6).

Table 3. Asymmetric epoxidation of cinnamyl alcohol **2c** in the presence of achiral diol additives and the optically active hydroperoxides (−)-**1a–d** as oxygen donors.

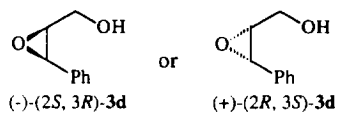


(-)-(2*S*, 3*S*)-**3c** (+)-(2*R*, 3*R*)-**3c**

entry	hydroperoxide	additive	t [h]	yield[a] [%]	ee[b] [%]	config.
1	(-)-(*S*)-**1a**	-	7	55	15	(+)-(2*R*, 3*R*)
2		*meso*-DET	9	41	0	
3		DHHM	5	49	7	(+)-(2*R*, 3*R*)
4	(-)-(*S*)-**1b**	-	7	35	12	(+)-(2*R*, 3*R*)
5		DHHM	5	38	9	(+)-(2*R*, 3*R*)
6	(-)-(*S*)-**1c**	-	7	52	10	(-)-(2*S*, 3*S*)
7		DHHM	7	32	9	(-)-(2*S*, 3*S*)
8	(-)-**1d**	-	160	32	6	(-)-(2*S*, 3*S*)
9		DHHM	160	54	24	(-)-(2*S*, 3*S*)

[a] Yield of isolated product after silica-gel chromatography; [b] determined by HPLC analysis on a chiral column (Chiracel OD); error ± 2% of the stated value.

Table 4. Asymmetric epoxidation of the (*Z*)-3-phenyl-2-propen-1-ol **2d** in the presence of the achiral additive DHHM and the optically active hydroperoxides (−)-(*S*)-**1a–c** as oxygen donors.

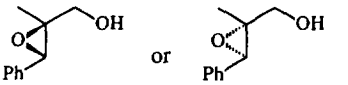


(-)-(2*S*, 3*R*)-**3d** (+)-(2*R*, 3*S*)-**3d**

entry	hydroperoxide	additive	t [h]	yield[a] [%]	ee[b] [%]	config.
1	(-)-(*S*)-**1a**	-	49	42	3	(+)-(2*R*, 3*S*)
2		DHHM	73	51	14	(-)-(2*S*, 3*R*)
3	(-)-(*S*)-**1b**	-	49	56	3	(-)-(2*S*, 3*R*)
4		DHHM	96	55	13	(-)-(2*S*, 3*R*)
5	(-)-(*S*)-**1c**	-	160	50	1	
6		DHHM	160	55	11	(-)-(2*S*, 3*R*)

[a] Yield of isolated product after silica-gel chromatography; [b] determined by HPLC analysis on a chiral column (Chiracel OD); error ± 2% of the stated value.

Table 5. Asymmetric epoxidation of α-methylcinnamyl alcohol **2e** in the presence of the achiral additive DHHM and the optically active hydroperoxides (−)-(*S*)-**1a–c** as oxygen donors.



(-)-(2*S*, 3*S*)-**3e** (+)-(2*R*, 3*R*)-**3e**

entry	hydroperoxide	additive	t [h]	yield[a] [%]	ee[b] [%]	config.
1	(-)-(*S*)-**1a**	-	6.5	80	28	(+)-(2*R*, 3*R*)
2		DHHM	6.5	66	34	(+)-(2*R*, 3*R*)
3	(-)-(*S*)-**1b**	-	6.5	83	31	(+)-(2*R*, 3*R*)
4		DHHM	6.5	89	34	(+)-(2*R*, 3*R*)
5	(-)-(*S*)-**1c**	-	9	82	19	(-)-(2*S*, 3*S*)
6		DHHM	9	42	5	(-)-(2*S*, 3*S*)

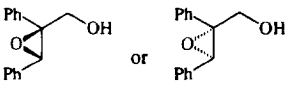
[a] Yield of isolated product after silica-gel chromatography; [b] determined by HPLC analysis on a chiral column (Chiracel OD); error ± 2% of the stated value.

Since in the asymmetric epoxidation of the diastereomeric phenyl-substituted allylic alcohols **2c,d** only low enantiomeric excesses were achieved (Tables 3 and 4), it was of interest to examine whether further substituents had a beneficial effect on the enantioselectivity. Therefore, α-methylcinnamyl alcohol **2e** was epoxidized by the hydroperoxides (−)-(*S*)-**1a,b** (Table 5). Analogous to the oxidation of cinnamyl alcohol **2c**, the cinnamyl derivative **2e** was attacked from the same enantiofacial side of the double bond to afford the (+)-(2*R*,3*R*)-**3c** as the main enantiomer. Also, the epoxidation of **2e** in the absence of an additive (Table 5, entries 1 and 3) gave the epoxide **3e** with ee values of 28 and 31%, which are twice those for the corresponding cinnamyl alcohol **2c**. The increase in the enantioselectivity is presumably due to the α-methyl substituent in this prochiral substrate. Unfortunately, these ee values could not be raised by the addition of the malonate DHHM (entries 2 and 4). When (−)-(*S*)-1-indanyl hydroperoxide **1c** was used, the reaction without additive led again to the opposite enantiomer, namely to (−)-(2*S*,3*S*)-**3c** with an ee value of 19% (entry 5). The addition of the malonate DHHM had no effect on the enantioselectivity (entry 6).

The fact that the α-methyl substituent in the allylic alcohol **2e** increased the ee values encouraged us to employ the sterically more demanding α-phenylcinnamyl alcohol **2f** as substrate. Unfortunately, its asymmetric epoxidation (Table 6) led in general to drastically decreased enantioselectivities (ee 2–6%). Also, the (*E*)-3-phenyl-2-buten-1-ol **2g**, for direct comparison with 3-methyl-2-buten-1-ol **2a** and geraniol **2b**, gave poor enantioselectivities (ee 2–21%) with the hydroperoxides (−)-(*S*)-**1a–c** (Table 7). On addition of the achiral malonate DHHM, a substantial increase of the ee values to 15–19% (entry 2 and 4) was achieved with the hydroperoxides (−)-(*S*)-**1a,b**, but the enantioselectivities were still too low for practical applications (entries 5 and 6).

It should be noticed that the oxygen transfer for the hydroperoxides (−)-(*S*)-**1a,b** occurs from the same enantiofacial side of the double bond in (*E*)-3-phenyl-2-buten-1-ol **2g** as in the substrates 3-methyl-2-buten-1-ol **2a** (Table 1) and geraniol **2b** (Table 2), which is contrary to the epoxidation of the cinnamyl alcohol **2c** (Table 3) and its α-substituted derivatives **2d,e** (Tables 4 and 5). This enantiofacial preference derives presumably from the second substituent at the 3-position in the allylic alcohols **2a,b,g**. Consequently, these results show that substitution of the (*E*)-methyl group in 3-methyl-2-

Table 6. Asymmetric epoxidation of α-phenylcinnamyl alcohol **2f** in the presence of the achiral additive DHHM and the optically active hydroperoxides (−)-(*S*)-**1a–c** as oxygen donors.

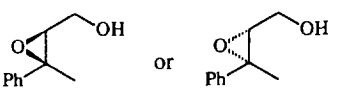


(+)-(2*S*, 3*S*)-**3f** (-)-(2*R*, 3*R*)-**3f**

entry	hydroperoxide	additive	t [h]	yield[a] [%]	ee[b] [%]	config.
1	(-)-(*S*)-**1a**	-	7.5	75	2	
2		DHHM	7.5	87	4	(-)-(2*R*, 3*R*)
3	(-)-(*S*)-**1b**	-	7.5	83	4	(-)-(2*R*, 3*R*)
4		DHHM	7.5	84	6	(-)-(2*R*, 3*R*)
5	(-)-(*S*)-**1c**	-	8	>95[c]	7	(+)-(2*S*, 3*S*)
6		DHHM	8	72[c]	8	(-)-(2*R*, 3*R*)

[a] Yield of isolated product after silica-gel chromatography; [b] determined by HPLC analysis on a chiral column (Chiracel OD); error ± 2% of the stated value; [c] conversion determined by ^{1}H NMR analysis of the crude reaction mixture; error ± 3% of the stated value; epoxide **3f** could not be seperated from 1-indanol, the reduction poduct of (-)-(*S*)-**1c**, by silica-gel chromatography.

Table 7. Asymmetric epoxidation of (*E*)-3-phenyl-2-buten-1-ol **2g** in the presence of the achiral additive DHHM and the optically active hydroperoxides (−)-(*S*)-**1a–c** as oxygen donors.



(-)-(2*S*, 3*S*)-**3g** (+)-(2*R*, 3*R*)-**3g**

entry	hydroperoxide	additive	t [h]	conv.[a] [%]	ee[b] [%]	config.
1	(-)-(*S*)-**1a**	-	9	69	2	
2		DHHM	9	68	21	(-)-(2*S*, 3*S*)
3	(-)-(*S*)-**1b**	-	9	53	6	(+)-(2*R*, 3*R*)
4		DHHM	9	77	15	(-)-(2*S*, 3*S*)
5	(-)-(*S*)-**1c**	-	168	60	7	(-)-(2*S*, 3*S*)
6		DHHM	168	69	9	(-)-(2*S*, 3*S*)

[a] Conversion, determined by ^{1}H NMR analysis on the crude reaction mixture; error ± 3% of the stated value; [b] determined by HPLC analysis on a chiral column (Chiracel OD); error ± 2% of the stated value.

buten-1-ol **2a** by a phenyl group causes the decrease in the enantioselectivity of the oxygen transfer, whereas a longer alkyl chain like in geraniol **2b** may be tolerated.

For the asymmetric epoxidation by the furan-derived hydroperoxide (−)-**1d**, only the model substrates 3-methyl-2-buten-1-ol **2a** and cinnamyl alcohol **2c** were used (Tables 1 and 3). Except for the epoxidation of cinnamyl alcohol **2c** in the presence of DHHM (ee 24%, cf. Table 3, entry 9), in all

cases the enantiomeric excesses (ee 2–21%) were below those obtained for the hydroperoxides (−)-(*S*)-**1a,b** (ee up to 49%). The addition of the malonate DHHM increased the ee values substantially (Table 1, entry 13 and Table 3, entry 9), but the enantioselectivities are still modest (ee <25%). Both allylic alcohols **2a** and **2c** were attacked by the hydroperoxide (−)-**1d** from the same side of the double bond. Thus, for the 3-methyl-2-buten-1-ol **2a** substrate, the furan-derived hydroperoxide (−)-**1d** behaves in its enantiofacial preference like the (−)-(*S*)-**1a,b** hydroperoxides, whereas in the oxidation of the cinnamyl alcohol **2c** it is akin to the more rigid indane-derived hydroperoxide (−)-(*S*)-**1c**. Disadvantageous are the long reaction times (ca. 7 days) and low yields in the epoxidation of cinnamyl alcohol **2c**, cf. entries 8 and 9 in Table 3, which must be due to unfavorable steric interactions in the transition state.

In summary, in regard to the substrate structure, among the differently substituted allylic alcohols examined, the highest enantioselectivities with ee values up to 50% were obtained in the epoxidation of the dialkyl-substituted 3-methyl-2-buten-1-ol **2a** and geraniol **2b**. The replacement of the (*E*)-alkyl group by a phenyl group resulted in a decrease in the ee values. The enantioselectivity could be raised by the introduction of an α-methyl group in cinnamyl alcohol **2c**, whereas the larger phenyl group caused the reactions to be nearly unselective. For the allylic alcohols **2a,b,g** with two substituents in the 3 position, the oxygen transfer by the hydroperoxides (−)-(*S*)-**1a,b** occurred from the same enantioface of the double bond, while the (*E*)-phenyl-substituted allylic alcohols **2c,e,f** were attacked at the opposite π face. The addition of the malonate-derived diol DHHM in catalytic amounts raised the enantiomeric excess from 20–30% to up to ee 50% in the epoxidation of the dialkyl-substituted 3-methyl-2-buten-1-ol **2a** and geraniol **2b** by the hydroperoxides (−)-(*S*)-**1a,b**; however, this additive showed no improvement in the enantioselectivity of the phenyl-substituted allylic alkohols **2c–g**. The more rigid (−)-(*S*)-1-indanyl hydroperoxide **1c** performed poorly even in the presence of the achiral malonate diol ligand DHHM. Without this additive, optically active hydroperoxide **1c** gave mainly the opposite enantiomer than in reactions with the hydroperoxides (−)-(*S*)-**1a,b**. Also, the use of ethyl 5-(1-hydroperoxy-ethyl)-2-methyl-furan-3-carboxylate **1d** led to only low enantioselectivities which could be raised up to fourfold by the addition of the malonate DHHM. On the basis of these results, namely ee values ≤50% in the asymmetric epoxidation of prochiral allylic alcohols **2**, the concept of employing optically active hydroperoxides as chiral oxygen donors even in the presence of achiral, multidentate, tartrate-akin ligands is not nearly as effective for enantioselective oxygen transfer as the by now classical Sharpless epoxidation, in which the *t*BuOOH as achiral oxygen donor and the C_2-symmetric tartrate as chiral auxiliary operate optimally.

Experimental

General

For the epoxidation reactions, all glassware was dried under vacuum (ca. 150°C/0.1 Torr) and all reactions were run under an argon gas atmosphere. CH_2Cl_2 was distilled under an argon gas atmosphere from calcium hydride. Horseradish peroxidase was purchased from Sigma (RZ 2.0). The hydroperoxides **1a–c** were prepared by a modified literature procedure,[6] hydroperoxide **1d** was synthesized according to literature.[7] (*Z*)-3-Phenyl-2-propen-1-ol **2d**,[6] α-methylcinnamyl alcohol **2e**,[10] α-phenylcinnamyl alcohol **2f**,[11] (*E*)-3-phenyl-2-buten-1-ol **2g**[12] and *meso*-DET[13] were synthesized according to literature.

Enantiomeric excesses of the hydroperoxides (−)-(*S*)-**1a–c** and (−)-**1d** and of all the phenyl-substituted epoxides **3c–g** were determined on the isolated product by HPLC analysis on chiral columns [Daicel Chiracel OD column, 25×0.46 cm] UV detection at 220 nm, *n*-hexane/isopropanol (9:1) as eluent, flow rates of 0.6 mL/min [hydroperoxides (−)-(*S*)-**1a,b**], 0.5 mL/min [hydroperoxide (−)-**1d**], 0.2 mL/min (epoxide **3g**), 0.8 mL/min (epoxides **3c–f**) or Daicel Chiracel OB-H column, same conditions as before except a flow rate of 0.5 mL/min [hydroperoxide (−)-(*S*)-**1c**)] or by MDGC

on a hexakis (2,3,6-tri-O-methyl)-β-cyclodextrin column in DB 1701, (25 m × 0.25 mm), at column temperature of 70°C for epoxide **3a** and 110°C for epoxide **3b**, with hydrogen as carrier gas.

Absolute configurations of the epoxides **3a–g** were assigned by direct comparison of the specific rotation determined on a polarimetric Chiralyser or on a polarimeter with the literature value.[2a,3,4a,6]

*General procedure for the resolution of hydroperoxides **1a–c** with HRP*

A mixture of the racemic hydroperoxide (30.0–45.0 mmol), 1.45–2.23 g guaiacol (12.0–18.0 mmol, 0.40 equiv.) and 60–90 mg HRP (1.50–2.25 μmol) in 375–450 mL 0.1 *M* phosphate buffer (pH 6.0) were stirred at room temperature (ca. 20°C) for at least 1 h. The enantiomeric excess of the hydroperoxide (−)-(*S*)-**1a–c** was checked by HPLC analysis on the chiral columns described above. When ee values >99% were achieved for the hydroperoxide, the reaction mixture was extracted with ethyl ether (5×70 mL) and the combined organic phases dried over $MgSO_4$. After evaporation of the solvent (20°C/20 Torr), the residue was purified by flash column chromatography [silica-gel, petroleum ether (30–35°C)/ethyl ether mixture of 9:1 to 8:2 for (−)-(*S*)-**1a, b** and 7:3 for (−)-(*S*)-**1c**]. The yields of the isolated hydroperoxides were between 33–44%.

*Ethyl (−)-5-(1-hydroperoxyethyl)-2-methylfuran-3-carboxylate **1d***

To a solution of 1.10 g (5.13 mmol) racemic hydroperoxide **1d** in 80 mL of a 1:1 mixture of 0.1 *M* phosphate buffer (pH 6.0) and ethanol were added 159 mg (1.28 mmol, 0.25 equiv.) guaiacol and 21.0 mg (0.525 μmol) HRP. After stirring for 1 h at room temperature (ca. 20°C), an ee value of >99% was obtained for the hydroperoxide (−)-**1d** (by HPLC analysis). The reaction mixture was worked up as described above and purified by flash column chromatography [silica gel, 2:1 petroleum ether (30–35°C)/ethyl ether]. At 52% conversion (as determined by ^1H NMR analysis on the crude reaction mixture) there were obtained as colourless solids 487 mg (2.27 mmol, 44%) of the hydroperoxide (−)-**1d**, $[\alpha]_D^{20}=-55.2$ (c 1.0 $CHCl_3$), >99% ee (determined by HPLC as described above) and 460 mg (2.32 mmol, 45%) of the corresponding (+)-alcohol, $[\alpha]_D^{20}=+8.8$ (c 1.0, $CHCl_3$)), 89% ee [determined by HPLC analysis on the Daicel Chiracel OB-H column with *n*-hexane/isopropanol (9:1) as eluent at a flow rate of 0.5 mL/min]. The spectral data match those reported in literature[7b] for the racemic compounds.

Diethyl 2-hydroxy-2-hydroxymethylmalonate (DHHM)[14]

A solution of 3.40 g (19.7 mmol) diethyl 2-methylene-malonate[8,15] in 10 mL acetone was slowly added dropwise at −30°C to a mixture of 3.54 g (22.4 mmol) potassium permanganate in 30 mL water and 70 mL acetone. After complete addition, the mixture was stirred for 45 min at −30°C, then for 2 h at 0°C. Manganese dioxide was removed by filtration over Celite and washed with acetone (5×20 mL). After evaporation of the solvent (35°C/20 Torr), the product was purified by silica-gel chromatography with ethyl ether as eluent. In this way, 1.05 g (5.09 mmol, 26%) of malonate DHHM were obtained as a colourless oil. ^1H NMR (200 MHz, $CDCl_3$): δ=1.30 (t, *J*=7.1 Hz, 6 H, 2×CH_3), 2.23 (t, *J*=7.0 Hz, 1 H, CH_2OH), 4.04 (s, 1 H, OH), 4.05 (d, *J*=7.0 Hz, 2 H, CH_2OH), 4.29 (q, *J*=7.1 Hz, 4 H, 2 x CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.9 (q, C-5), 62.8 (t, C-4), 64.6 (t, C-2), 79.3 (s, C-1), 168.8 (s, C-3); IR (neat): ν=3480 cm^{-1} (O–H), 3000, 2950, 2890 (C–H), 1750 (C=O), 1460, 1380, 1315, 1250, 1160, 1110, 1085, 1050, 935, 870. Anal. Calcd for $C_8H_{14}O_6$ (MW 206.2): C, 46.60; H, 6.84. Found: C, 46.29; H, 6.60.

*General procedure of the epoxidation of the allylic alcohols **2a–g** with the optically active hydroperoxides (−)-(S)-**1a–c** and (−)-**1d** in the presence of additives*

A Schlenk tube was charged with ca. 50 mg activated 4Å molecular sieves and 2.0 mL (in the reactions with 3-methyl-2-buten-1-ol **2a** and geraniol **2b**) or 1.5 mL CH_2Cl_2 (in the reactions with the phenyl-substituted allylic alcohols **2c–g**). The mixture was cooled to −20°C and 14.7 μL (0.050 mmol) Ti(O*iPr*)$_4$ and 120 μL (0.060 mmol, in the reactions with 3-methyl-2-buten-1-ol **2a** and geraniol **2b**) or 150 μl (0.075 mmol, in the reactions with the phenyl-substituted allylic alcohols **2c–g**) of a 0.500

M solution of the diols ethylene glycol, pinacol, *meso*-DET and DHHM in CH_2Cl_2 were added. After stirring for 10 min at −20°C, a solution of the hydroperoxide (1.20 mmol) in 1 mL CH_2Cl_2 was added and the reaction mixture was stirred for 30 min at −20°C. The neat allylic alcohols (1.00 mmol) (3-methyl-2-buten-1-ol **2a** and geraniol **2b**) or as a solution in 1 mL CH_2Cl_2 (phenyl-substituted allylic alcohols **2c–g**) were added. The reaction mixture was then stirred for the times stated in the tables at −20°C. The reaction progress was monitored by ^{1}H NMR analysis directly on the reaction mixture. For workup, the catalyst was destroyed by the addition of 50 μL aqueous, saturated NH_4F solution and stirred for 1 h at room temperature (ca. 20°C). After removal of the suspended material by filtration over Celite and thorough washing of the residue with CH_2Cl_2 (5×1 mL), the solvent was evaporated (20°C/20 Torr). The epoxides were isolated by flash column chromatography [silica gel, various mixtures of petroleum ether (30–50°C)/ethyl ether]. Since the epoxide **3g** is prone to decomposition, it was isolated once for characterization and otherwise the conversion (by ^{1}H NMR analysis) and enantiomeric excess were determined directly on the crude reaction mixture. The spectral data for the epoxides **3a–g** match those reported.[2a,3,9,16,17] The enantiomeric excess was determined as described above.

*General procedure of the epoxidation of the allylic alcohols **2a–g** with the optically active hydroperoxides (−)-(S)-**1a–c** and (−)-**1d***

The reactions were conducted as described above without the addition of any diol additives.

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