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# Biocatalytic kinetic resolution of hydroperoxy vinylsilanes by horseradish peroxidase (HRP) and lipases, a comparative study

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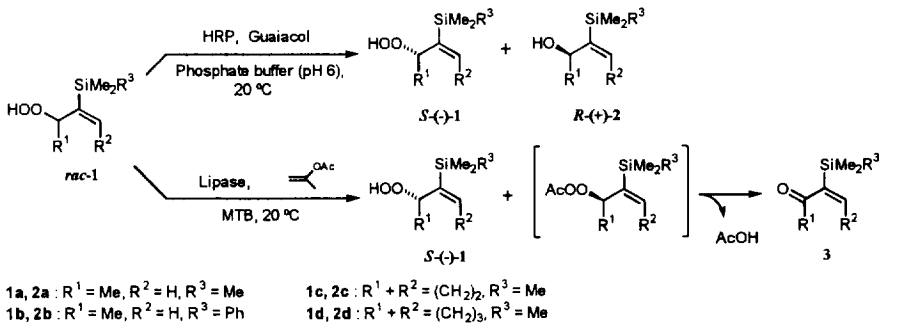
***Abstract:*** The kinetic resolution of hydroperoxy vinylsilanes **1** has been investigated by the horseradish-peroxidase(HRP)-catalyzed reduction with guaiacol and by the acetylation with isopropenyl acetate in the presence of various lipases. The best results (ee values up to 89% at 48% conversion) were obtained for the lipase-catalyzed reactions. © 1997 Elsevier Science Ltd

Hydroperoxides, when activated by metal catalysts, are important oxidants in organic synthesis.[1] Although optically active hydroperoxides should be of interest as potential asymmetric oxygen-transfer reagent, to date their preparation is limited. Recently, some progress in this direction has been achieved through the enzymatic kinetic resolution of chiral hydroperoxides. For example, in one of the earliest studies, Baba *et al.* reported on the enantioselective acetylation of hydroperoxides with isopropenyl acetate in the presence of lipases.[2] Hydroperoxides were also resolved by chloroperoxidase(CPO)-catalyzed asymmetric sulfoxidation of prochiral sulfides in moderate ee values.[3] We have recently developed a method for the enantioselective reduction of racemic hydroperoxides by HRP in the presence of guaiacol,[4] a process which yielded better enantioselectivities.[5] To compare the synthetic scope of HRP and lipases, we have now investigated the kinetic resolution of hydroperoxy vinylsilanes **1** with these two enzyme systems (Scheme 1).




**Scheme 1.** HRP- and lipase-catalyzed kinetic resolution of hydroperoxy vinylsilanes **1**.

The resulting optically active allyl hydroperoxides **1**, as well as the corresponding allylic alcohols **2**, are useful chiral building blocks, as they may be functionalized in numerous ways through appropriate transformation of the trimethylsilyl group[6] and converted diastereoselectively to epoxy alcohols by Ti(IV)-catalyzed oxyfunctionalisation.[7]

The racemic hydroperoxy vinylsilanes **1** were prepared from commercially available starting materials according to the synthesis formerly developed by us.[8] The results of the kinetic resolution of allyl hydroperoxides **1** by HRP-catalyzed enantioselective reduction with guaiacol are listed in Table 1.

The HRP-catalyzed reduction of the silyl-substituted allyl hydroperoxides **1** proceeded rather slowly since usually the kinetic resolution of hydroperoxides by HRP is accomplished within a few hours;[4,5] in

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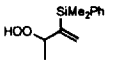
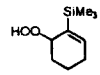
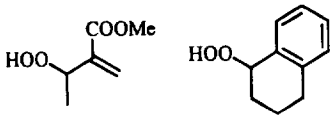
**Table 1.** Enantioselectivities of the HRP-catalyzed kinetic resolution of hydroperoxy vinylsilanes **1**

| Entry | Substrate | [mmol] | Substrate Ratio HRP[c] | Guaiacol | Time [d] | Conv.[a] [%] | ee[b] [%] ROOH **1**[d] | ROH **2**[e] | E[f] |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | 2.50 | 2000:1 | 1:1 | 7 | 42 | 42 | 58 | 5.6 |
| 2 | | 0.06 | 500:1 | 1:1 | 2 | 58 | 58 | 42 | 4.2 |
| 3 |  | 0.68 | 1500:1 | 1:1 | 16 | 51 | 75 | 73 | 14.2 |
| 4 |  | 2.32 | 3500:1 | 1.5:1 | 21 | 69 | 55 | 25 | 2.7 |
| 5 | | 1.20 | 1140:1[g] | 1:1 | 4 | 64 | 74 | 42 | 5.1 |
| 6 |  | 0.32 | 1000:1 | 1:1 | 27 | 0 | -- | -- | -- |

[a] Calculated from c = ee(alcohol) / [ee(alcohol) + ee(acetate)] (see Ref. 9); the product mixture also contained 5 to 10% silyl enone **3**. [b] Enantiomeric excess (ee) determined by GC analysis on a permethylated β-cyclodextrin column (30% on OV 1701, 30 m, 0.25 mm ID; $H_2$ gas) for the alcohols **2a** [40 °C (1 min) → 5 °C/min → 60 °C], **2c** (60 °C isotherm) and **2d** (90 °C isotherm) and by HPLC on a Daicel Chiralcel OD-H column [eluent: *n*-hexane/*iso*-propyl alcohol (99:1); flow rate 0.3 mL $min^{-1}$] for the alcohol **2b**; the hydroperoxides **1** were reduced to the corresponding alcohols **2** after preparative chromatographic separation from the latter. [c] HRP was obtained from Sigma [200 U/mg (purpurogallin)] and used as received. [d] Absolute configuration *S*-(−); assigned according to Ref. 10. [e] Absolute configuration *R*-(+); assigned according to Ref. 10. [f] Enantiomeric ratio measures the preference of the enzyme for one enantiomer over the other (see Ref. 9). [g] HRP was obtained from Boehringer Mannheim [250 U/mg (guaiacol)] and used as received.

fact, the six-membered-ring cyclic hydroperoxy vinylsilane **1d** (entry 6) was not transformed by HRP at all. The enantiomeric excesses (ee values) at a conversion of ca. 50% were moderate to good, the best result (ee values of ca. 75%) was obtained for the dimethylphenyl-substituted vinylsilane **1b** (entry 3). The long reaction times as well as the moderate ee values are attributed to the steric hindrance of the bulky spherical silyl group. For comparison, the hydroperoxides **4**[4] and **5**[5] are excellent substrates for the enzyme HRP, presumably because the flat nature of the carbomethoxy group in **4** and the benzo annelation in **5** are sterically less demanding. This also explains why the hydroperoxy vinylsilane **1b**, which carries the sterically more demanding dimethylphenylsilyl group, is significantly less reactive than the trimethylsilyl derivative **1a** (cf. entries 1 and 3). The higher enantioselectivity for the less reactive substrate **1b** may be rationalized in terms of the better enantiodifferentiation by the enzyme due to the greater steric demand of the dimethylphenylsilyl group.

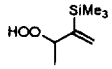
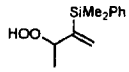
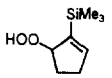
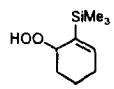



**4** **5**

For comparison, the kinetic resolution of the hydroperoxy vinylsilanes **1** by the lipase-catalyzed enantioselective acetylation has been investigated (Table 2). The intermediary peracetates formed in the lipase-catalyzed acetylation of the allylic hydroperoxides **1** (cf. Scheme 1) do not persist under the reaction conditions, instead the corresponding enones **3** were observed. The formation of enones from secondary peracetates of allylic hydroperoxides is a well-documented reaction.[11]

The enzyme screening revealed that the acetylation of the allyl hydroperoxides **1** with the lipases CCL (from *Candida cylindracea*) and PCL (from *Pseudomonas cepacia*) were also very slow, but for

**Table 2.** Enantioselectivities in the lipase-catalyzed kinetic resolution of hydroperoxy vinylsilanes **1**

| Entry | Substrate | Lipase | Substrate[a] [mmol] | Lipase [mg] | Time [d] | Conv.[b] [%] | ee [%][c] ROOH **1** | Config.[d] | E[e] |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  | CCL[f] | 0.147 | 134 | 19 | 52 | 36 | *R*-(+) | 2.8 |
| 2 | | PCL[g] | 0.149 | 100 | 22 | 48 | 89 | *S*-(-) | 165 |
| 3 | | BSL[h] | 0.115 | 20.0 | 5 | 67 | <5 | *S*-(-) | - |
| 4 |  | CCL[f] | 0.096 | 48.0 | 29 | 38 | 20 | *R*-(+) | 2.4 |
| 5 | | PCL[g] | 0.090 | 40.1 | 29 | 31 | 33 | *S*-(-) | 9.0 |
| 6 | | BSL[h] | 0.101 | 22.0 | 21 | 59 | 13 | *S*-(-) | 1.3 |
| 7 |  | CCL[f] | 0.157 | 50.0 | 21 | 11 | <5 | *R*-(+) | - |
| 8 | | PCL[g] | 0.120 | 43.3 | 26 | 73 | 74 | *S*-(-) | 3.5 |
| 9 | | BSL[h] | 0.136 | 17.8 | 5 h | 38 | 30 | *S*-(-) | 3.9 |
| 10 |  | PCL[g] | 0.104 | 43.8 | 26 | 41 | 43 | *S*-(-) | 6.4 |
| 11 | | BSL[h] | 0.516 | 100 | 1 | 45 | 63 | *S*-(-) | 14.6 |

[a] The molar ratio of hydroperoxy vinylsilane **1** and isopropenyl acetate was 3 to 10. [b] Determined on the $^1$H NMR spectrum of the product mixture. [c] Determined as described in footnote b of Table 1. [d] The absolute configuration was assigned according to Ref. 10. [e] Enantiomeric ratio measures the preference of the enzyme for one enantiomer over the other (see Ref. 9). [f] Lipase from *Candida cylindracea* (Sigma). [g] Lipase from *Pseudomonas cepacia* (Fluka). [h] Lipase from *Burkholderia species* (CHIRAZYME® L-1, Boehringer Mannheim).

the hydroperoxy vinylsilane **1a** an ee value of 89% was obtained at a conversion of 48% (entry 2). The reactions with the lipase BSL (from *Burkholderia species*), on the contrary, were several orders of magnitude faster, while the lipase PPL (from *Porcine pancreas*) showed no conversion within 7 d for the hydroperoxides **1a** and **1c** (data not shown). The six-membered-ring cyclic substrate **1d**, which was not at all accepted by the enzyme HRP, was resolved by the lipase BSL with an ee value of 63% at a conversion of 45% (entry 11). These reactions are the first examples of the kinetic resolution of chiral hydroperoxides, in which lipases as biocatalysts afford better enantioselectivities than HRP. Compared with the resolution of the corresponding alcohols **2**,[10] however, the hydroperoxides **1** are worse substrates for the lipase-catalyzed acetylation. This is expected since the additional oxygen atom enlarges the distance between the chirality center and the reacting functionality; nevertheless, the reaction rates are much faster due to the greater nucleophilicity of the hydroperoxides.

In conclusion, the present comparative study of HRP *versus* lipases demonstrates that for the kinetic resolution of chiral hydroperoxides, the lipases are the enzymes of choice for the transformation of sterically demanding substrates which are not or only reluctantly converted by HRP. The results for the different lipases display, however, that the enantioselectivities for the hydroperoxy vinylsilanes **1** are significantly lower than for the corresponding alcohols **2**.[10] An effective enzyme system for the kinetic resolution of sterically encumbered chiral hydroperoxides is, therefore, yet to be found.

*General procedure for the preparative-scale, HRP-catalyzed reduction*

The hydroperoxy vinylsilane (±)-**1a–c** (1.00 mmol) and guaiacol (1.00 mmol) were dissolved in 20 mL 0.1 M phosphate buffer (pH 6) and subsequently (0.3–2)×$10^{-3}$ mmol HRP was added. The reaction mixture was stirred at 20°C until ca. 50% conversion and then extracted with ethyl ether (3×40 mL). The combined organic phases were decanted from the red guaiacol polymer, dried over $MgSO_4$, and the solvent evaporated (0°C/12 Torr). The products were separated by flash chromatography [20 mg silica gel 0.063–0.200 mm, 9:1 petroleum ether (30–50°C): ethyl ether] to afford the enantiomerically enriched hydroperoxy vinylsilanes *S*-(−)-**1a–c** and the corresponding alcohols *R*-(+)-**2a–c** in yields between 39 and 62% (based on 50% substrate conversion).

*General procedure for the semipreparative-scale, lipase-catalyzed acetylation*

To a solution of the hydroperoxy vinylsilane (±)-**1d** (0.50 mmol) in 10 mL methyl *tert*-butyl ether were added 1.5 mmol of isopropenyl acetate and 100 mg BSL lipase powder. The heterogeneous mixture was vigorously stirred at 20°C until 50% conversion, the enzyme was removed by centrifugation and the solvent was evaporated (20°C/12 Torr). The products were separated by flash chromatography [10 g silica gel, 15:1 petroleum ether (30–50°C): ethyl ether] to afford the enantiomerically enriched hydroperoxy vinylsilanes *S*-(−)-**1d** in 48% yield (based on 50% substrate conversion).

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