Pergamon

Tetrahedron Letters 39 (1998) 2945–2946

TETRAHEDRON LETTERS

Horseradish peroxidase: An effective but unselective biocatalyst for biaryl synthesis

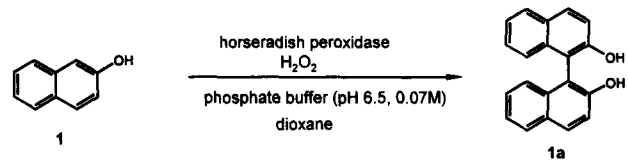
Marko M. Schmitt, Ellen Schüler, Myriam Braun, Dietmar Häring and Peter Schreier*

Lehrstuhl für Lebensmittelchemie, Universität Würzburg,
Am Hubland
D-97074 Würzburg, Germany

Received 9 February 1998; accepted 2 March 1998

Abstract: The oxidative dimerization of phenolic and naphtholic compounds catalyzed by horseradish peroxidase was investigated. Contrary to Sridhar et al. [*Tetrahedron Lett.*, **1997**, 38, 5695-5696] exclusively racemic biaryl compounds were identified.

Atropselective synthesis of biaryls is still a challenging field. As oxidoreductases may play a central role in the biogenesis of biaryls, we studied the potential of horseradish peroxidase (HRP; EC 1.11.1.7) for catalyzing oxidative dimerization reactions. HRP has been established as an effective biocatalysator for oxidoreductions in organic synthesis: a variety of substrates are oxidized by using hydrogen peroxide or organic hydroperoxides [1]. Recently, we published the results of the HRP-catalyzed reduction of secondary hydroperoxides in the presence of guaiacol to provide optically active alcohols and hydroperoxides with enantiomeric excesses (ee) up to 99 % [2]. In our present work, we focused on the oxidative coupling of phenolic compounds by HRP-catalysis which leads to biaryls.



1 1a

Scheme 1: Oxidative dimerization of 2-naphthol **1** by horseradish peroxidase catalysis

To assess the enantioselectivity of the HRP-catalyzed biaryl coupling we selected four model compounds shown in Table 1. Oxidation of substrates **1-4** led to the corresponding biaryls by symmetric coupling in ortho position to the hydroxy group as shown in Scheme 1 [3]. The ee-values and signs of optical rotation of the biaryls **1a** and **2a** were determined by HPLC on chiral phases. A photodiode array detector, coupled with a polarimetric ChiraLyser detector, was employed to ascertain the configuration of the enantiomers. As a representative example, Figure 1 shows the corresponding chromatograms for HRP-synthesized biaryl **1a**. The enantiomeric analysis of products **3a** and **4a** was performed by CD spectroscopy and measurement of the optical rotation. The yields of the products and their enantiomeric distributions are summarized in Table 1. All biaryls were obtained as racemic products.

0040-4039/98/$19.00
PII: S0040-4039(98)00526-7

Table 1: Oxidative dimerization of naphthols and phenols catalyzed by horseradish peroxidase

Substrate	Yield (%) of biaryls **1a-4a**	% ee
2-Naphthol **1**	35	< 5 %[a]
6-Hydroxyquinoline **2**	60	< 5 %[b]
Methyl 3-hydroxy-2-naphthoate **3**	20	< 5 %[c]
2,3,5-Trimethylphenol **4**	10	< 5 %[c]

[a] HPLC on Ceramospher RU-1 (Shiseido, Japan); [b] HPLC on Chiralcel OD-H (Daicel, USA);
[c] CD spectroscopy and measurement of optical rotation

Variation of the experimental conditions such as change of pH-value (5-8) and temperature, or use of organic cosolvents (10-90 % acetonitrile, acetone, dioxane) or chiral solvating agents did not influence the selectivity of the HRP-catalyzed biaryl coupling. Thus, HRP is an effective but unselective biocatalyst for the synthesis of biaryls.

Our results are completely inconsistent with those recently reported by Sridhar et al. [4]. Converting 2-naphthol with HRP in the presence of hydrogen peroxide, these authors have described 1,1′-binaphthol with an ee of 52 % (*R*), determined solely by measuring the optical rotation of the isolated product. We were not able to reproduce this result taking advantage of the more sophisticated chiral phase HPLC. Hence, we exclude an enantiomeric preference of HRP for biaryl coupling. This conclusion is confirmed by the results of our extended studies of HRP-catalyzed biaryl synthesis [5] and fits well to the recently published findings of Davin et al. [6]. Based on the characterization of a "dirigent protein", these authors have suggested "capture" of phenoxy radical intermediates during peroxidase catalysis, inducing atropselective coupling of biaryls.

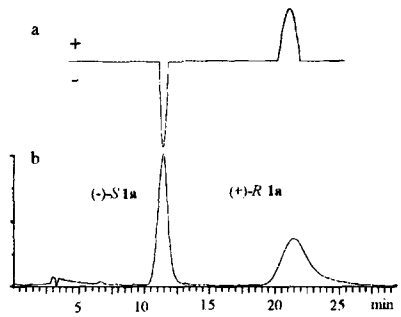


Figure 1: HPLC analysis of (-)-*S* and (+)-*R*-1,1′-binaphthol **1a**, formed by horseradish peroxidase-catalyzed oxidative dimerization of substrate **1**. (a) polarimetric ChiraLyser detection (b) UV-detection (254nm); column: Ceramospher RU-1 (Shiseido, Japan), eluent: methanol; flow: 1ml/min; temperature 50°C

Acknowledgement: The Deutsche Forschungsgemeinschaft (SFB 347) is thanked for financial support.

References and Notes:

1. Dawson, J. H.; *Science*, **1988**, *240*, 433-439.
2. Adam, W.; Hoch, U.; Lazarus, M.; Saha-Möller, C. R.; Schreier, P.; *J. Am. Chem. Soc.*, **1995**, *117*, 11898-11901.
3. The enzymatic oxidation of substrates **1-4** (100-200mg per 100ml) was performed with horseradish peroxidase (25mg type II from Sigma, USA per 100ml) in 0.07M phosphate buffer at pH 6.5 with 20% v/v dioxane as organic cosolvent and equivalent amount of 1.5% H_2O_2 at 20 °C. After a reaction time of 15-60 minutes the products were extracted with diethyl ether, dried (Na_2SO_4) and evaporated in vacuo. Purification was performed by silica gel column chromatography.
4. Sridhar, M.; Vadivel, S. K.; Bhalerao, U. T.; *Tetrahedron Lett.*, **1997**, *38*, 5695-5696.
5. Schmitt, M. M.; Doctoral Thesis, Universität Würzburg, **1998**.
6. Davin, L. B.; Wang, H.-B., Crowell A. L.; Bedgar D. L.; Martin, D. M.; Sarkanen, S.; Lewis, N.G.; *Science*, **1997**, *275*, 362-366.