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Enantioselective oxidative coupling of 2-naphthol derivatives catalyzed by *Camellia sinensis* cell culture

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Abstract—Optically active 1,1′-binaphthyl-2,2′-diols were synthesized by oxidative coupling of 2-naphthols using *Camellia sinensis* cell culture as a catalytic system.

1,1′-Binaphthalene derivatives have been widely used in organic synthesis as chirality inducers for highly stereoselective reactions.[1] Enantiomerically pure binaphthyl derivatives have been prepared by optical resolution of racemic compounds,[2] an intermolecular Ullmann coupling,[3] a nucleophilic aromatic substitution,[4] an oxidative dimerization of 2-naphthols with copper(II) amine complexes as oxidant[5] or electrocatalytic oxidative coupling.[6]

Development of the usage of enzymes for oxidation reactions aimed at green chemistry is significant these days. Horseradish peroxidase (HRP) is a commercially available metalloporphyrin enzyme and has been established as an effective biocatalyst for organic and inorganic oxidation reactions by using hydrogen peroxide or hydroperoxides. Recently, this enzyme has once again come into focus with the discovery of its remarkable enantioselective reactions, viz., 1) enantioselective oxidation of unsymmetrical sulfides to sulfoxides,[7] 2) enantioselective reduction of racemic hydroperoxides to alcohols[8] and 3) enantioselective oxidation of 2-naphthols to 1,1′-binaphthyl-2,2′-diols.[9] Sridhar et al. reported a novel enantioselective oxidation of 2-naphthols to (*R*)-1,1′-binaphthyl-2,2′-diol catalyzed by HRP (Y. 75%, 52% ee).[9] Contrary to this report, Schreier et al.[10] published that the HRP is an effective but unselective biocatalyst for biaryl synthesis, where the oxidative dimerization of 2-naphthol catalyzed by HRP to 1,1′-binaphthyl-2,2′-diol resulted in 35% chemical yield with <5% ee.

Keywords: asymmetric oxidative coupling; chiral binaphthol; catalysts; enzymes and enzyme reaction.

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Recently, we have found that *Camellia sinensis* cell culture is an efficient source of peroxidase (POD) enzymes. We have established *C. sinensis* cell culture systems with high POD activity and applied them to the oxidative coupling of dibenzylbutanolides with quantitative yield.[11] In this work, we would like to report our investigation of enantioselective oxidative coupling of 2-naphthol derivatives by *C. sinensis* cell culture.

Oxidative coupling of 2-naphthol (**1a**) was first examined. The oxidative coupling reaction was performed at 25°C by three methods, that is: [A] with freely suspended *C. sinensis* cell culture in B5 medium[12] at pH 5.4 and in the stationary phase after 12 days of incubation in the presence of H_2O_2, [B] with immmobilized *C. sinensis* cell culture (ICSC) in B5 medium in the absence of foreign hydrogen peroxide or [C] with ICSC in hexane in the absence of foreign hydrogen peroxide. The results are summarized in Table 1.

In the case of method A, the reactions were performed under various H_2O_2 concentrations. Both optical and chemical yields increased with increasing H_2O_2 content, and maximum optical yield (59%) and chemical yield (47%) were obtained with 0.5 mL of 30% H_2O_2 (entry 3). At 30% H_2O_2 contents of 1.0–6.0 mL, optical yields and chemical yields decreased. The shortened reaction time caused the better optical yields (entries 2–6), which decreased for the longer time by more than 12 min. Interestingly, (*R*)-1,1′-binaphthyl-2,2′-diol (**2a**) was produced as the sole product, which was isolated in 47% yield after chromatographical purification. The enantiomeric excess was determined to be 59% by HPLC analysis using a chiral column and the absolute configuration was assigned as *R* by comparison of the retention time of the authentic sample. In the case of

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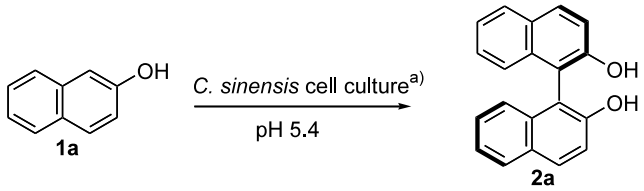
Table 1. Asymmetric oxidative coupling of 2-naphthol with *C. sinensis* cell culture[a]



1a 2a

Entry	Method	H_2O_2 (mL)	Time (h)	Yield[b] (%)	%ee	Confign[c]
1	A	0	24	0	–	–
2	A	0.3% 1.0	0.2	5	4	*R*
3	A	30% 0.5	0.2	47	59	*R*
4	A	30% 1.0	0.2	40	30	*R*
5	A	30% 2.0	0.2	31	24	*R*
6	A	30% 6.0	0.2	10	15	*R*
7	B	0	24	6	32	*R*
8	C	0	24	16	22	*R*

[a] 50 mL.
[b] Isolated yields.
[c] Assignment by comparison with the authentic sample.

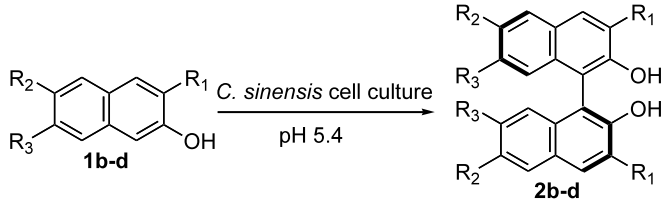
methods [B] and [C], **2a** was given in the absence of foreign hydrogen peroxide, but both chemical and optical yields were poor compared with the method of entry 3.

According to the established procedure above, various 2-naphthol derivatives were subjected to oxidative coupling reaction with *C. sinensis* cell culture. These results are summarized in Table 2. Introduction of Br, OMe or COOMe groups to the naphthalene ring decreased enantioselectivity and chemical yield. To our surprise, the coupling of **1b–d** with *C. sinensis* cell culture yielded **2b–d** with the opposite stereochemistry to that of **2a**.

In summary, a novel enantioselective oxidative coupling of 2-naphthol derivatives by *C. sinensis* cell culture with high POD activity can be achieved in this work. It is noteworthy that moderate to good ee values were obtained for simple substrates such as 2-naphthol (CY 47%, OY 59%) that are difficult substrates for enantioselective oxidative coupling reaction.[5] Further studies on enantioselective oxidative coupling are now in progress.

For a typical experiment, the suspension-cultured cells which had originally been isolated from *C. sinensis* as described in our previous papers were used.[11,13–17] ICSC were prepared according to the following procedure. Freely suspended *C. sinensis* (4.6 g cells and 20 mL broth) and 60 ml B5 medium in the stationary phase after 12 days of incubation were mixed with 5% sodium alginate solution (80 mL). The resultant mixture was dropped into a 0.6% $CaCl_2$ solution (1000 mL) and rinsed with water to give ICSC. ICSC (including 7 g

Table 2. Asymmetric oxidative coupling of 2-naphthols with *C. sinensis* cell culture



1b-d 2b-d

Entry	Naphthol, **1**	Method	H_2O_2 (mL)	Time (h)	Yield (%)[a]	% ee	Config.[b]
1	**1b** ($R_1=R_3=H$, $R_2=Br$)	A	30% 0.5	1	28	36	*S*
2	**1b**	B	0	48	12	8	*S*
3	**1b**	C	0	48	32	6	*S*
4	**1c** ($R_1=R_2=H$, $R_3=OCH_3$)	A	30% 0.5	1	34	16	*S*
5	**1c**	B	0	96	6	6	*S*
6	**1c**	C	0	96	8	0	–
7	**1d** ($R_1=COOCH_3$, $R_2=R_3=H$)	A	30% 0.5	1	0	–	–
8	**1d**	B	0	72	10	32	*S*
9	**1d**	C	0	72	6	10	*S*

[a] Isolated yields.
[b] Assignment by comparison of optical rotations with the values in the literature. **2b**,[5a] **2c**,[5d] **2d**.[5d]

cells and 30 mL broth) was added to freshly prepared B5 medium (80 mL per flask) and was shaken on a rotary shaker (110 rpm) in the dark at 25°C. A substrate (35 mg) was added to the freely suspended plant cell cultures (19 g cells and 80 mL broth), ICSC cells (including 7 g cells and 30 mL broth) in 80 mL freshly B5 medium or ICSC cells (including 7 g cells and 30 mL broth) in 20 mL hexane. After regular intervals of incubation, the incubation mixture was filtered, the filtered cells or immmobilized cells were washed with AcOEt, and the filtrates were combined. The combined mixture was extracted with AcOEt. The organic layer was dried over anhydrous $MgSO_4$. In the case of reaction in hexane, homogenated cells were extracted with AcOEt.

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