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Cyanobacterium-catalyzed asymmetric reduction of ketones

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Abstract

Synechococcus sp. PCC 7942, a cyanobacterium, acted as a biocatalyst to reduce aryl methyl ketones into the corresponding (*S*)-alcohols with excellent enantioselectivities under illumination.

Keywords: asymmetric reduction; enantioselectivity; cyanobacteria; algae; phototroph.

The asymmetric reduction of prochiral ketones has been extensively explored by researchers using chemical and biological methods. As the latter method, microbial reduction has been widely used for the synthesis of chiral alcohols.[1–3] On the contrary, the use of photosynthetic plant cells and algae for asymmetric reduction is relatively rare[4–10] due to the difficulty in their cultivation, the low reactivity of plant cells, and the lack of knowledge on the stereochemical control of reactions. Thus, a new photosynthetic biocatalyst with high reactivity and selectivity for reducing ketones is now unavailable.

Here we report our finding that *Synechococcus* sp. PCC 7942, a cyanobacterium which belongs to phototroph, could enantioselectively reduce several aryl methyl ketones to the corresponding (*S*)-alcohols with the aid of light (Fig. 1).

When 2′,3′,4′,5′,6′-pentafluoroacetophenone (**1**) was reacted in a suspension culture of *Synechococcus* sp. PCC 7942 under illumination, it was completely consumed within 3 days, and the corresponding (*S*)-alcohol was obtained in a good chemical yield (>90%) with excellent enantiomeric excess (ee) (>99%).

Optically active alcohols having pentafluorophenyl moiety are potentially useful chiral building blocks for drugs, insecticides, and ferroelectric liquid crystals.[11,12] Fluorine substitutions of hydrogen atoms in the molecules tend to dramatically influence the biological activity or the molecular reactivity. The perfluorinated phenyl group has a striking stacking ability with electron-rich arenes. For example, hexafluorobenzene was reported to form an 1:1 molecular

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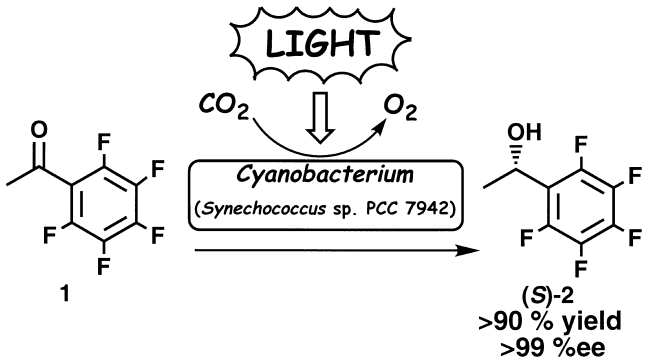


Figure 1. Asymmetric reduction of 2′,3′,4′,5′,6′-pentafluoroacetophenone by *Synechococcus* sp. PCC 7942. The alga absorbs light and carbon dioxide and uses this energy to reduce **1** into optically pure **2**

complex with benzene.[13] In optically active pentafluorophenyl compounds, the pentafluorophenyl group is reported to be stacked with a naphthalene ring.[11,14]

As shown in Table 1, other aryl methyl ketones were also reduced by *Synechococcus* sp. PCC 7942, and all the ketones were reduced with high enantioselectivities (> 96% ee). Although the chemical yields on the reduction of several ketones were not satisfactory, the elongation of incubation times enabled us to improve the chemical yields in the reduction of *o*- and *p*-chloroacetophenone by the alga.

Thus, the cyanobacterium is found to enantioselectively reduce various aryl methyl ketones. The merits of using the cyanobacterium in biotransformation are summarized as follows:

(a) **Low biocatalyst/substrate (b/s) ratio**: A large amount of a biocatalyst is usually required to reduce a considerable amount of a substrate (the b/s for baker's yeast is about 50–350).[15] On the contrary, only 37 mg (dry weight) of the alga could reduce 0.57 mmol (120 mg) of **1** in 9 days. Thus, a low b/s ratio (2.6 wet weight, 0.5 dry weight) could be achieved. The improvement in the b/s ratio is caused by the fact that the cyanobacterium can utilize the power of light effectively to reduce the substrate.

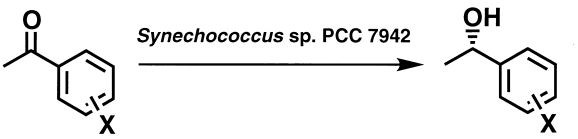
(b) **High selectivity and wide substrate specificity**: Ketones used in this report are reduced by the cyanobacterium with excellent enantioselectivities (> 96%). An enzyme exhibiting high enantioselectivity usually shows a relatively strict substrate specificity; hence, there scarcely is a catalyst that reacts with many kinds of substrates and also shows high selectivities. This alga can reduce a wide variety of aryl methyl ketones and afford the corresponding alcohols with high enantioselectivities.

(c) **Easy manipulation and high growth rate**: Photosynthetic plant cell cultures typically grow quite slowly. However, cyanobacteria grow much faster than plant cell cultures in spite of the fact that the algae are types of phototroph. Thus, contamination with microbes during the cultivation can be eliminated.

(d) **Ecological system**: To date, cyanobacteria have been used for biomass production[16] and biologically produced electricity.[17] We propose that cyanobacteria can also be used efficiently as biocatalysts; the algae have the ability to directly utilize sunlight and carbon dioxide for photosynthesis. Due to this activity, cyanobacteria may help to solve a global environmental problem—the greenhouse effect—which increasingly threatens mankind at the beginning of the 21st century.

Reduction of **1** with *Synechococcus* sp. PCC 7942: Mature cultured algae (1.5 mL) of *Synechococcus* sp. PCC 7942 were transferred to 300 mL Erlenmeyer flasks containing BG-11

Table 1
Reduction of acetophenone derivatives by *Synechococcus* sp. PCC 7942



X	*Yield (%)*	*Ee (%)*	*Config.*
H[a)]	3	96	*S*
o-Cl[a)]	24	96	*S*
o-Cl[b)]	51	98	*S*
m-Cl[a)]	37	100	*S*
p-Cl[a)]	34	96	*S*
p-Cl[b)]	84	98	*S*
o-Me[a)]	8	100	*S*
m-Me[a)]	31	99	*S*
p-Me[a)]	6	100	*S*
o-OMe[a)]	10	100	*S*
m-OMe[a)]	19	100	*S*
p-OMe[a)]	4	100	*S*
o-F[a)]	28	100	*S*
m-F[a)]	14	100	*S*
p-F[a)]	2	100	*S*

Reaction conditions: Substrate; 50 mg/L, Cyanobacterium+Medium; 100 mL, 1000 lux, a) Reaction time; 3 days, b) Reaction time; 9 days

medium (100 mL). After pre-cultivation for about 14 days under fluorescent lamp illumination (1000 lux) at 20°C, 0.57 mmol of **1** was added to the flask. The mixture was incubated for 3 days under illumination at 20°C. The mixture was then extracted with ether three times. The conversion (90%) and enantiomeric excess (>99%) of the alcohol were determined by using GC-analysis (GC conditions: CP-cyclodextrin-B-2,3,6-M-19; 25 m; He 2 mL/min, 120°C, ketone; 2.9 min, *R*-alcohol; 5.8 min, *S*-alcohol; 6.3 min). The ether layer was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography (eluent: hexane:ethyl acetate = 10:1) followed by distillation with Kügelrohr apparatus affording pure **2** in a 50% chemical yield with >99% ee.

The product was identified with ^{1}H NMR, IR, and an elemental analysis. The absolute configuration of the alcohol was determined to be *S* by comparing the optical rotational value with that reported. $[\alpha]_D^{20}$ –6.40 (*c* 0.50, pentane) (lit.[18] (*S*)-2, $[\alpha]_D^{20}$ –6.33 (*c* 1.01, pentane)).

References

1. Roberts, S. M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 611–633.
2. Azerad, R. *Bull. Soc. Chim. Fr.* **1995**, *132*, 17–51.
3. Faber, K. *Biotransformations in Organic Chemistry, 2nd ed.*; Springer: Berlin, 1995.
4. Suga, T.; Hirata, T. *Phytochem.* **1990**, *29*, 2393–2406.
5. Alfermann, A. W.; Reinhard, E. *Bull. Soc. Chim. Fr.* **1980**, *II*, 35–45.
6. Shimoda, K.; Hirata, T. *J. Mol. Cat. B: Enzymatic* **2000**, *8*, 255–264.
7. Noma, Y.; Asakawa, Y. *Phytochem.* **1992**, *31*, 2009–2011.
8. Nakamura, K.; Miyoshi, H.; Sugiyama, T.; Hamada, H. *Phytochem.* **1995**, *40*, 1419–1420.
9. Kuramoto, T.; Iwamoto, K.; Izumi, M.; Kirihata, M.; Yoshizako, F. *Biosci. Biotechnol., Biochem.* **1999**, *63*, 598–601.
10. Yamazaki, Y.; Maruyama, A.; Hosono, K.; Higashihara, T.; Kobayashi, H. Z. *Naturforsch.* **1993**, *48c*, 451–456.
11. Sakai, T.; Miki, Y.; Nakatani, M.; Ema, T.; Uneyama, K.; Utaka, M. *Tetrahedron Lett.* **1998**, *39*, 5233–5236.
12. Sakai, T.; Miki, Y.; Tsuboi, M.; Takeuchi, H.; Ema, T.; Uneyama, K.; Utaka, M. *J. Org. Chem.* **2000**, *65*, 2740–2747.
13. Patric, C. R.; Prosser, G. S. *Nature* **1960**, *187*, 1021–1021.
14. Li, Z.-T.; Becher, J. *Synlett* **1997**, 557–560.
15. Bucciarelli, M.; Forni, A.; Moretti, I.; Torre, G. *Synthesis* **1983**, 897–899.
16. Partensky, F.; Hess, W. R.; Vaulot, D. *Microbiol. Mol. Biol. Rev.* **1999**, *63*, 106–127.
17. Yagishita, T.; Sawayama, S.; Tsukahara, K.; Ogi, T. *Bioelectrochem. Bioenerg.* **1977**, *43*, 177–181.
18. Nakamura, K.; Matsuda, T. *J. Org. Chem.* **1998**, *63*, 8957–8964.