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Highly enantioselective bioreduction of 2-fluorocinnamyl alcohols mediated by *Saccharomyces cerevisiae*

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ABSTRACT

Biocatalytic reduction of 2-fluorocinnamyl alcohols mediated by *Saccharomyces cerevisiae* was investigated in phosphate buffer solutions. Product analysis clearly showed that (*S*)-2-fluoro-3-arylpropanols were afforded in high yields with up to 92% ee value.

Optically active fluorinated organic compounds have received much attention of many chemists for their practical importance in the pharmaceutical industry.[1] Although a variety of preparative methods had been established in the past decades,[2] few reports were concerned with the creation of a chiral carbon center linking with only one fluorine atom by catalytic asymmetric reduction. One efficient route via iridium-catalyzed asymmetric hydrogenation of fluorinated olefins using N-, P-ligands has been published by Andersson and his co-workers.[3] For metal-catalyzed hydrogenation, the cleavage of C–F bond took place competitively as the main side-reaction.[4]

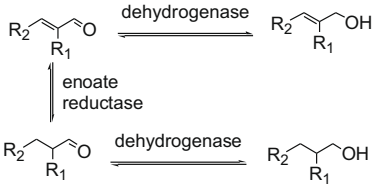
Recently, the stereoselective bioreduction of C=C bonds with electron-withdrawing groups mediated by *Saccharomyces cerevisiae* was successfully applied to construct chiral carbon centers.[5] For instance, unsaturated conjugated aldehydes were easily reduced to their corresponding saturated alcohols with high enantioselectivities.[6] However, there is a certain limitation for this bioreduction to prepare chiral primary alcohols due to the considerably competitive formation of allyl alcohols, though good yields of saturated alcohols were observed in a few cases.[7] The proposed mechanism for the bioreduction of enals was outlined in Scheme 1.[8]

Since the conversion of saturated aldehydes into primary alcohols usually proceeds quickly, the products distribution is dependent on the relative reduction rate between C=O bond and C=C bond of enals. The key factor to determine the amount of saturated alcohol in equilibrium is the reverse transformation rate from the allyl alcohol to the enal. However, it still remains elusive how the substituents at both α- and β-sites affect the bioreduction of allyl alcohols.

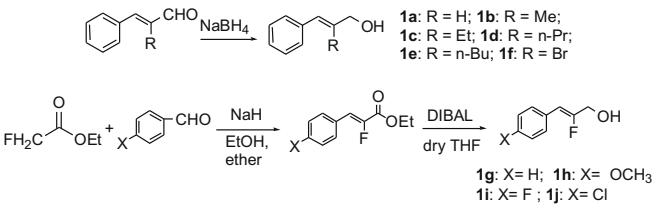
Considering the unique property of fluorine atom, namely, its small size and high negativity, we are interested in elucidating the electronic and steric effects of substituents, especially fluorine atom on the bioreduction of allyl alcohols into the saturated alcohols. In the present study, we described a convenient synthetic method of chiral-fluorinated primary alcohols via the reduction of 2-fluorocinnamyl alcohols mediated by *Saccharomyces cerevisiae*.

Cinnamyl alcohols **1a–j** were chosen as the substrates in this work, where **1a–f** were obtained by reducing the corresponding aldehydes with $NaBH_4$, and 2-fluoro-3-aryl-2-propen-1-ols (**1g–j**) were prepared by the condensation of ethyl fluoroacetate with substituted benzaldehydes and the subsequent reduction with DIBAL (Scheme 2). The preparative procedures and all the spectrum data of these compounds were provided in Supplementary data.

Bioreduction was carried out by shaking a mixture of the substrate **1** and dry baker's yeast (Angel instant dry yeast) in sodium phosphate buffer solution (PBS) at 30 °C (Scheme 3). Products were purified by silica gel column chromatography and characterized



Scheme 1.



Scheme 2.

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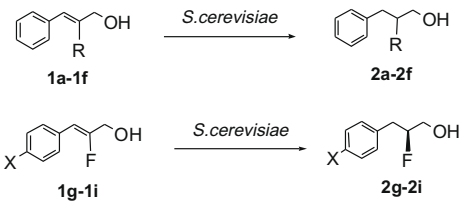

Scheme 3.

Table 1
Bioreduction of **1a–g** with dry baker's yeast[a]

Entry	Substrate	Time (h)	Product	Yield[b] (%)
1	**1a**	24	**2a**	99
2	**1b**	24	**2b**	57 (58)
3	**1c**	24	**2c**	20
4	**1d**	24	**2d**	9
5	**1e**	24	**2e**	0
6	**1f**	48	**2f**	5
7	**1g**	24	**2g**	61 (99)

[a] **1** (50 mg), pH 7.5 PBS (20 mL), baker's yeast (2.0 g) at 30 °C.
[b] Yields determined by GC, and the data in parentheses for 48 h.

carefully, indicating that the saturated alcohol **2** was the main product. The reactions are shown in Scheme 3.

The product yields were determined by GC and calculated based on the amount of the substrate **1** added. All the results are summarized in Table 1.

First the steric effect of α-substituents of cinnamyl alcohols was investigated. As shown in Table 1, cinnamyl alcohol **1a** was consumed completely within 24 h, giving the product **2a** almost quantitatively (entry 1). When the substrate **1b** (R = CH_3) was used, only 57% of **2b** was detected due to the low conversion rate (Table 1, entry 2). With the increase of the size of R group, the conversion sharply declined (Table 1, entries 3–5). For example, **1e** (R = C_4H_9) was too sterically hindered to be reduced within 24 h.

On the other hand, the electronic effect of α-substituents was also assessed by using 2-halocinnamyl alcohols **1f** and **1g** as the substrates. Although the size of bromine atom was near to ethyl group, the yield for **2f** was only 5% (Table 1, entry 6), which was much lower than that for **2c** in the parallel experiments. Similarly, when hydrogen atom was replaced by fluorine atom with near size, only 61% of **1g** was converted into the saturated alcohol **2g** after 24 h (Table 1, entry 7). Moreover, a marked reactivity difference was also observed between **1g** and **1b**. When the reaction was prolonged to 48 h, **1g** was quantitatively converted into the saturated alcohol **2g** (Table 1, entry 7), but the yield for **2b** was almost kept constant (Table 1, entry2). These results strongly indicated that dehydrogenation of allyl alcohols was not only very sensitive to the steric hindrance of R group, but was also affected by its electronic effect to a certain content. The inhibitive role for halogen atoms could be attributed to their high negative inductive effect that decreased the electron density on C=C double bond of **1f** and **1g**. In addition, the stereochemistry for this bioreduction of **1b** or 2-methylcinnamaldehyde mediated by baker's yeast had been studied, and the (*S*)-isomer was preferentially afforded.[9] In fact, the formation of (*S*)-isomer was almost preferred in the bioreduction of other allyl alcohols.[10] Similarly, the absolute configuration of **2g** was determined to be *S* by comparing its optical rotation with the literature data[3b], whereas the configurations of **2c**, **2d,** and **2f** were not determined for their low conversions.

Apart from the marked effect of α-substitutes, the role for substituents at β-site was also estimated. Thus the bioreduction of several fluorinated cinnamyl alcohols **1g–j** with different substituents on benzene ring was studied. The reduction reaction of **1g–j**

Table 2
Bioreduction of **1g–j** with dry baker's yeast[a]

Entry	**1** (loading)	Product	Yield[c] (%)	ee[d] (%)	$[\alpha]_D^{25}$
1	**1g** (50 mg)	**2g**	99	81	−14.5°
2	**1h** (50 mg)	**2h**	41	nd	nd
3	**1h** (27 mg)	**2h**	90	87	nd
4[b]	**1h** (27 mg)	**2h**	96	88	−10.9°
5[b]	**1i** (27 mg)	**2i**	95	82	−43.6°
6[b]	**1j** (27 mg)	**2j**	27	nd	nd

[a] BY (2.0 g), pH 7.5 PBS (20 mL), at 30 °C, 48 h.
[b] 0.1 mL of *n*-butanol (5.5×10^{-5} mol l^{-1}) was added.
[c] Determined by GC.
[d] Determined by chiral HPLC using Chiralpak AS-H column.

was carried out under the conditions as noted in Table 2, and the reaction time was prolonged to 48 h owing to the slow rate. The ee values for products **2g–i** were determined by chiral HPLC. As a consequence, **1g** was completely converted into **2g** with 81% ee (Table 2, entry 1). Under the same conditions, **1h** with an electron-donating methoxy group was reduced slowly and only 41% of **2h** was generated after 48 h (Table 2, entry 2). However, the yield of **2h** was raised to 90% when the amount of **1h** was reduced from 50 mg to 27 mg (entry 3). In order to improve the solubility of the solid substrate **1h** during the reaction, a certain amount of *n*-butanol was added as the co-solvent. In this case, **1h** was almost completely converted into **2h** (entry 4). Similar results were also observed in the case of *p*-fluorocinnamyl alcohol **1i** (Table 2, entry 5). It should be emphasized that a marked difference in reactivity was observed between **1i** and *p*-chlorocinnamyl alcohol **1j**. In the latter case, only 27% of **2j** was yielded after 48 h (Table 2, entry 6). As reported, the Hammett constant for *p*-Cl is 0.23, and that for *p*-F is 0.06. These results indicated that the electronic property of β-substituents of allyl alcohols also had a considerable effect on their bioreduction. Obviously, the electron-withdrawing β-substituent would retard the biocatalytic dehydrogenation of allyl alcohols to some extent. Moreover, the configuration of the new compounds **2h** and **2i** was assigned to be *S* by determining their optical rotation degrees and by characterizing the structures of their Mosher esters. As shown in Table 2, all the three products **2g**, **2h**, and **2i** are levorotatory although their rotation degrees are different. The analysis of ^1H and ^{19}F NMR spectra data of the Mosher esters prepared from the optically active compounds **2g**, **2h**, and **2i** and their corresponding racemates clearly indicated that the configurations of **2h** and **2i** were the same as that of **2g**.[11]

Next, the effect of pH value of the phosphate buffer solution was studied. As shown in Table 3, the conversion rate for **1h** was somewhat dependent on the pH value, and a relatively low conversion was observed in the pH 6.5 phosphate buffer (entry 1). However, the effect of pH value on the enantioselectivity was ignorable. Another interesting result was observed by changing the amount of baker's yeast. When the amount was reduced from 2.0 g to 0.5 g, **1h** could also be quantitatively converted into the product **2h**, and the ee value increased from 88% to 92% (Table 3, entry

Table 3
Effect of pH and the amount of baker's yeast on bioreduction of **1h**[a]

Entry	pH	BY (g)	Yield (%) for **2h**	ee (%)
1	6.5	2.0	75	86
2	7.0	2.0	96	88
3	7.5	2.0	96	88
4	7.0	1.0	96	91
5	7.0	0.5	96	92
6	7.0	0.3	91	90

[a] **1h** (27 mg), PBS (20 mL), 30 °C, 48 h; 0.1 mL of *n*-butanol added. Yields determined by GC, and ee by chiral HPLC.

5). A decline in conversion appeared when the amount of baker's yeast decreased to 0.3 g (entry 6).

In conclusion, the baker's yeast-mediated reduction of 2-fluorocinnamyl alcohols was a convenient way to prepare a chiral center containing a fluorine atom with high stereoselectivity. This method can avoid the cleavage of C–F bond during reduction. Substituents both at α- and β-sites had a significant influence on the bioreduction of allyl alcohols.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.01.073.

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11. The Mosher esters were prepared by the reaction of (R)-(+)-Mosher acid chloride with **2** in the presence of Et_3N. Apparent differences were observed in chemical shifts of the stereomers of these Mosher esters. The changes in chemical shifts of the methoxy group for ^1H NMR and in chemical shifts of fluoro group for ^{19}F NMR were typical. δ: 3.575 and 3.565 (OCH_3, s) for Mosher ester of racemic **2g**, 3.575 for (*S*)-**2g**; 184.59–184.94 and 185.04–185.42 (F, m) for Mosher ester of racemic **2g**, 184.59–184.94 for (*S*)-**2g**. δ: 3.574 and 3.563 (OCH_3, s) for Mosher ester of racemic **2h**, 3.574 for (*S*)-**2h**; 184.59–184.94 and 185.04–185.51 (F, m) for Mosher ester of racemic **2h**, 184.59–184.94 for (*S*)-**2h**. δ: 3.574 and 3.561 (OCH_3, s) for Mosher ester of racemic **2i**, 3.574 for (*S*)-**2i**; 185.10–185.52 and 185.59–186.21 (F, m) for Mosher ester of racemic **2i**, 185.16–185.52 for (*S*)-**2i**.