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Enantioselective bioreduction of 2-fluoro-2-alken-1-ols mediated by *Saccharomyces cerevisiae*

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ABSTRACT

Biocatalytic reduction of 2-fluoro-2-alken-1-ols mediated by *Saccharomyces cerevisiae* underwent smoothly and yielded (*S*)-2-fluorinated alkanols with high enantioselectivities. The conversion rate was markedly depending on the configuration of alkene moiety of the substrate, the chain length of alkyl group at β position of C=C bond, as well as the reaction conditions.

1. Introduction

The asymmetric bioreduction of C=C bond is an important method for constructing chiral carbon centers [1–5]. For instance, *Saccharomyces cerevisiae* (baker's yeast) mediated bioreduction of enals usually produces chiral primary alcohols with high to excellent stereoselectivity [6–9]. However, only a few cases of enals could be reduced into the saturated alcohols in high yields [10–12]. As shown in Scheme 1, the reductions of C=O bond and C=C bond usually proceed competitively during the bioreduction of enals mediated by baker's yeast [13].

When the C=C bond of the enal is preferentially reduced by enoate reductase, the saturated aldehyde generated *in situ* would be further converted into the saturated alcohol quickly. It is clear that the low yield of saturated alcohols is caused mainly by the competitive formation of the allyl alcohols via the fast reduction of C=O bond initiated by dehydrogenase. The key factor to affect the ratio of saturated alcohols in equilibrium of bioreduction is the reverse transformation rate from the allyl alcohols to the enals. Recently, asymmetric bioreduction of activated alkenes is successfully performed by using isolated or cloned enoate reductases [EC 1.3.1.x] from the "old yellow enzyme" family [14–17]. For examples, the use of OYE 1-3 and KYE1 from yeast can not only drastically increase the chemo- and stereoselectivities, but also greatly improve the yields [18–21].Based on the previous reports [6,10,22], we realize that the property of substituents at both α and β sites plays an important role in determining the reverse transformation rate of the allyl alcohols to the enals during the bioreduction mediated by baker's yeast. Our earlier work also shows that the size of substituent at α position strongly affects the conversion rate from allyl alcohols to saturated alcohols [23]. With the increasing of the size of R_1 group, the conversion rate sharply declines.

In order to develop one efficient synthetic way of optically pure fluorinated primary alcohols, we have already studied the baker's yeast mediated bioreduction of 2-fluorocinnamyl alcohols [23]. Because of its small size near to a hydrogen atom, fluorine atom at α position of cinnamyl alcohols makes the bioreduction more achievable than other α substituent cinnamyl alcohols and a high yield of chiral fluorinated primary alcohols was afforded with high enantioselectivities. This observation encourages us to investigate the effect of R_2 group systematically. Although we have reported that the conversion is markedly affected by the substituent on the benzene ring [23], it is still kept unclear how the configuration of 2-fluoroallyllic alcohols and the alkyl chain length of R_2 group affect the bioreduction mediated by baker's yeast. In the present work, we investigated the substrate spectrum in more detail by switching the (*E*/*Z*) configuration of the alkene moiety and changing the alkyl groups at β position of C=C bond to broaden the applicability of bioreduction of 2-fluoroallylic alcohols.

2. Experimental

2.1. General

All NMR spectra were recorded on a Bruker AV-400MHz spectrometer (Bruker Co., Switzerland) with TMS as the internal

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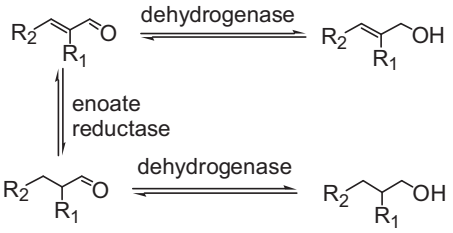


Scheme 1.

standard. Optical rotation was measured by JASCO P1010 polarimeter (JASCO Co., Japan) in the solvent indicated. Flash column chromatography was carried out using 300–400 mesh silica gel (Qingdao Haiyang Chemical Co. Ltd., China). For thin-layer chromatography (TLC), silica gel plates (GF254) were used. HPLC analysis was performed on a Shimadzu LC-10 chromatograph (Shimadzu Co., Japan) with SPD-10AV UV-VIS Detector. Chiralpak AS-H was purchased from Daicel Chemical Industries Ltd. (Japan). Conversions and yields were determined by FuLi gas chromatograph (Fuli Analytical Instruments Co. Ltd., China). (*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid was purchased from Alfa Aesar China Co. Ltd. (China). Baker's yeast (Angel instant dry yeast) was purchased from Angel Yeast Co. Ltd. (China). Solvents were purified by standard procedures and distilled before use. Reagents and starting materials purchased from commercial suppliers were used without further purification unless otherwise stated.

2.2. Procedures for preparing (Z)-ethyl 2-fluoro-3-(4-methoxyphenyl)-2-propenoate [(Z)-**1a**] and ethyl 2-fluoro-4-methyl-2-pentenoate (**1b**)

To 7.2 g NaH and 0.6 mL abs. ethanol in 150 mL dry ether, ethyl fluoroacetate (14.7 mL 150 mmol) and aldehyde (150 mmol) were added dropwise at 15 °C during about 2 h with stirring, and the mixture was stirred for 4–6 h. The reaction was quenched with aqueous NH_4Cl (100 mL), and extracted with ether (3× 100 mL). The organic layer was washed with sat. NaCl (3× 100 mL), dried over anhydrous sodium sulfate and evaporated under reduced pressure.

2.2.1. (Z)-Ethyl 2-fluoro-3-(4-methoxyphenyl)-2-propenoate [(Z)-**1a**]

Product was collected at 155–160 °C/6–7 mmHg (13.4 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.2 Hz, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.34 (q, *J* = 7.2 Hz, 2H, CH_2), 6.87 (d, *J* = 35.6 Hz, 1H, CH), 6.92 (d, *J* = 8.8 Hz, 2H, Ar), 7.60 (d, *J* = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 55.3, 61.7, 114.3, 117.5 (d, *J* = 5 .0 Hz), 123.9 (d, *J* = 4.3 Hz), 132.0 (d, *J* = 8.2 Hz), 145.9 (d, *J* = 262.2 Hz), 160.7 (d, *J* = 3.4 Hz), 161.7 (d, *J* = 33.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −128.8 (d, *J* = 35.3 Hz).

2.2.2. Ethyl 2-fluoro-4-methyl-2-pentenoate (**1b**)

Product was collected at 102–106 °C/40 mmHg (7.2 g, 30%) which is a mixture with a ratio of *E*:*Z* = 15:85. ^{1}H NMR (400 MHz, $CDCl_3$): (*Z*)-isomer: δ 1.07 (d, *J* = 6.8 Hz, 6H, $2CH_3$), 1.33 (t, *J* = 7.2 Hz 3H, CH_3), 2.86 (m, 1H, CH), 4.27 (q, *J* = 7.2 Hz, 2H, CH_2), 5.98 (dd, *J* = 33.6 Hz and *J* = 9.6 Hz, 1H, CH); (*E*)-isomer: δ 1.07 (d, *J* = 6.8 Hz, 6H, $2CH_3$), 1.33 (t, *J* = 7.2 Hz 3H, CH_3), 3.35 (m, 1H, CH), 4.27 (q, *J* = 7.2 Hz, 2H, CH_2), 5.73 (dd, *J* = 22.0 Hz and *J* = 10.4 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.0 (d, *J* = 1.7 Hz), 22.7 (d, *J* = 2.3 Hz), 24.6 (d, *J* = 2.4 Hz), 61.5, 127.1 (d, *J* = 11.2 Hz), 146.5 (d, *J* = 253.4 Hz), 161.1 (d, *J* = 35.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): (*Z*)-isomer: δ −131.5 (d, *J* = 34.2 Hz); (*E*)-isomer: δ −124.9 (d, *J* = 19.9 Hz).

2.3. Procedure for preparing ethyl 2-fluoro-3-(4-methoxyphenyl)-2-propenoate [**1a** (*E*:*Z* = 3:1)]

Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (10 g, 41 mmol) was dissolved in dry THF under N_2. The solution was cooled to 0 °C and *n*-BuLi (2.5 M, 16.5 mL) was added. The solution was stirred for 1 h at 0 °C. *p*-Methoxybenzaldehyde (4.1 mL, 34 mmol) was added and the solution was left over night at room temperature. The reaction was quenched with water (100 mL), extracted with CH_2Cl_2 (3× 100 mL), dried over $MgSO_4$ and evaporated. The product was separated by column chromatography (petroleum ether:ethyl acetate, 30:1), yielding a mixture of ethyl 2-fluoro-3-(4-methoxyphenyl)-2-propenoate with a ratio of *E*:*Z* = 3:1 (4.3 g, 56%).

^{1}H NMR (400 MHz, $CDCl_3$): (*Z*)-isomer: δ 1.37 (t, *J* = 7.2 Hz, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.34 (q, *J* = 7.2 Hz, 2H, CH_2), 6.87 (d, *J* = 35.6 Hz, 1H, CH), 6.92 (d, *J* = 8.8 Hz, 2H, Ar), 7.60 (d, *J* = 8.8 Hz, 2H, Ar); (*E*)-isomer δ: 1.29 (t, *J* = 7.2 Hz, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.26 (q, *J* = 7.2 Hz, 2H, CH_2), 6.84 (d, *J* = 23.6 Hz, 1H, CH), 6.87 (d, *J* = 8.8 Hz, 2H, Ar), 7.51 (d, *J* = 8.8 Hz, 2H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): (*Z*)-isomer: δ −128.8 (d, *J* = 35.3 Hz); (*E*)-isomer: δ −119.2 (d, *J* = 27.0 Hz).

2.4. Procedure for preparing (Z)-ethyl 2-fluoro-2-hexenoate (**1c**)

Ethyl 2-(diethoxyphosphoryl)-2-fluoroacetate (4.8 g, 20.0 mmol) was evacuated pump for 15 min, dissolved in dry THF, transferred to a dried round bottomed flask and cooled to −40 °C. 2.5 M *n*-BuLi (8.4 mL) was added. After being stirred for 1 h at −40 °C, Butyryl chloride (2.2 mL, 21.0 mmol) was added and the mixture was stirred for 4 h at room temperature. The reaction was quenched with H_2O (50 mL), extracted with CH_2Cl_2 (3× 50 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The oily residue was purified by silica gel column chromatography (petroleum ether:ethyl acetate, 5:1–1:1) to afford triethyl 2-fluoro-3-oxo-2-phosphono-hexanoate (4.37 g, 70%) as a colorless oil. Triethyl 2-fluoro-3-oxo-2-phosphono-hexanoate was dissolved in ethanol (80 mL) and cooled to −78 °C. Sodium borohydride (532 mg, 14 mmol) was added in ethanol (20 mL) and the solution was stirred for 1 h at −78 °C, then for 4 h at room temperature. It was quenched with NH_4Cl (aq, satd., 100 mL), extracted with CH_2Cl_2, dried over $MgSO_4$, evaporated. The residue was dissolved in CH_2Cl_2, washed with water (to remove inorganic salts), dried over $MgSO_4$ and evaporated. The crude oil was purified by column chromatography (petroleum ether:ethyl acetate, 50:1), yielding the pure (*Z*)-ethyl 2-fluoro-2-hexenoate (0.9 g, 40%).

2.4.1. (Z)-Ethyl 2-fluoro-2-hexenoate (**1c**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (t, *J* = 7.2 Hz, 3H, CH_3), 1.32 (t, *J* = 7.2 Hz, 3H, CH_3), 1.47 (m, 2H, CH_2), 2.20 (m, 2H, CH_2), 4.27 (q, *J* = 7.2 Hz, 2H, CH_2), 6.11 (dt, *J* = 33.2 Hz and *J* = 8.0 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 14.1, 21.6 (d, *J* = 1.9 Hz), 26.2 (d, *J* = 2.5 Hz), 61.5, 120.5 (d, *J* = 12.0 Hz), 148.1 (d, *J* = 254.0 Hz), 160.9 (d, *J* = 35.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −131.0 (d, *J* = 31.2 Hz).

2.4.2. (Z)-Ethyl 6-chloro-2-fluoro-2-hexenoate (**1d**)

The product was purified by column chromatography (petroleum ether:ethyl acetate, 50:1). Overall yield is 40%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.2 Hz, 3H, CH_3), 1.95 (m, 2H, CH_2), 2.45 (m, 2H, CH_2), 3.58 (t, *J* = 6.4 Hz, 2H, CH_2), 4.30 (q, *J* = 7.2 Hz, 2H, CH_2), 6.13 (dt, *J* =32.8 Hz and *J* = 8.0 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 21.7 (d, *J* = 3.0 Hz), 31.1 (d, *J* = 2.0 Hz), 44.0, 61.7, 118.5 (d, *J* = 11.5 Hz), 148.7 (d, *J* =256.0 Hz), 160.6 (d, *J* = 35.1 Hz); ^{19}F NMR (376 MHz, CDCl3): δ −129.1 (d, *J* = 33.1 Hz).

*2.4.3. (Z)-Ethyl 2-fluoro-2-octenoate (**1e**)*

The product was purified by column chromatography (petroleum ether:ethyl acetate, 50:1). Overall yield is 45%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.91 (t, J = 6.8 Hz, 3H, CH_3), 1.35 (t, J = 7.2 Hz, 3H, CH_3), 1.30–1.36 (m, 8H, $4CH_2$), 1.46 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 4.29 (q, J = 7.2 Hz, 2H, CH_2), 6.14 (dt, J = 33.2 Hz and J = 8.0 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 14.1, 22.3, 24.2 (d, J = 2.5 Hz), 28.0 (d, J = 1.9 Hz), 31.3, 61.5, 120.8 (d, J = 11.0 Hz), 148.0 (d, J = 253.0 Hz), 161.0 (d, J = 36.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −131.2 (d, J = 34.2 Hz).

*2.4.4. (Z)-Ethyl 2-fluoro-2-decenoate (**1f**)*

The product was purified by column chromatography (petroleum ether:ethyl acetate, 50:1). Overall yield is 42%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H, CH_3), 1.25–1.31 (m, 12H, $6CH_2$), 1.33 (t, J = 7.2 Hz, 3H, CH_3), 1.44 (m, 2H, CH_2), 2.23 (m, 2H, CH_2), 4.27 (q, J = 7.2 Hz, 2H, CH_2), 6.13 (dt, J = 33.6 Hz and J = 7.6 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 22.6, 24.2 (d, J = 2.5 Hz), 28.4 (d, J = 1.8 Hz), 28.9, 29.2, 31.7, 61.5, 120.8 (d, J = 11.7 Hz), 148.0 (d, J = 253.3 Hz), 161.0 (d, J = 35.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −131.1 (d, J = 33.1 Hz).

*2.4.5. (Z)-Ethyl 2-fluoro-2-tetradecenoate (**1g**)*

The product was purified by column chromatography (petroleum ether:ethyl acetate, 50:1). Overall yield is 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H, CH_3), 1.26–1.35 (m, 16H, $8CH_2$), 1.34 (t, J = 7.2 Hz, 3H, CH_3), 1.43 (m, 2H, CH_2), 2.25 (m, 2H, CH_2), 4.29 (q, J = 7.2 Hz, 2H, CH_2), 6.13 (dt, J = 33.6 Hz and J = 7.6 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 14.2, 22.7, 24.2 (d, J = 2.5 Hz), 28.4 (d, J = 1.8 Hz), 29.2, 29.3 (d, J = 1.8 Hz), 29.5, 29.6, 31.90, 61.4, 120.8 (d, J = 12.0 Hz), 148.0 (d, J = 253.0 Hz), 160.9 (d, J = 36.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −131.1 (d, J = 33.4 Hz).

*2.5. Procedures for preparing 2-fluoro-4-methyl-2-penten-1-ol (**2b**)*

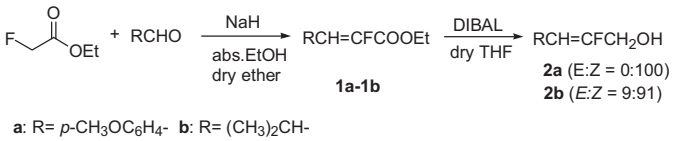
To the solution of ethyl 2-fluoro-4-methyl-2-pentenoate (32 mmol) in dry THF (200 mL), DIBAL (1.23 M in hexane, 96 mmol) was added at 0 °C. The solution was stirred at room temperature for 4 h, quenched with Rochelles salt under vigorous stirring, extracted with CH_2Cl_2 (3× 100 mL), washed with water (2× 100 mL), dried over $MgSO_4$ and evaporated.

*2.5.1. (Z)-2-Fluoro-3-(4-methoxyphenyl)-2-propen-1-ol [(Z)-**2a**]*

Purification by silica gel column chromatography (petroleum ether:ethyl acetate, 8:1) gave white solid (70% yield); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 160 °C. The retention time for (*Z*)-**2a** was 15.25 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16 (br, 1H, OH), 3.83 (s, 3H, OCH_3), 4.28 (d, J = 15.2 Hz, 2H, CH_2), 5.73 (d, J = 38.8 Hz, 1H, CH), 6.89 (d, J = 8.8 Hz, 2H, Ar), 7.47 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 62.0 (d, J = 31.0 Hz), 107.2 (d, J = 7.0 Hz), 113.9, 125.4 (d, J = 3.0 Hz), 130.0 (d, J = 8.0 Hz), 156.9 (d, J = 263.0 Hz), 158.9; ^{19}F NMR (376 MHz, $CDCl_3$): δ −116.1 (m).

*2.5.2. (E)-2-Fluoro-3-(4-methoxyphenyl)-2-propen-1-ol [(E)-**2a**]*

Purification by silica gel column chromatography (petroleum ether:ethyl acetate, 10:1) gave pure (*E*)-**2a** (80%); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 160 °C. The retention time for (*E*)-**2a** was 10.557 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.72 (br, 1H, OH), 3.81 (s, 3H, OCH_3), 4.36 (d, J = 22.4 Hz, 2H, CH_2), 6.38 (d, J = 20.0 Hz, 1H, CH), 6.88 (d, J = 8.8 Hz, 2H, Ar), 7.17 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.3, 58.5 (d, J = 29.5 Hz), 111.1 (d, J = 26.2 Hz), 114.1, 125.3 (d, J = 12.3 Hz), 129.8 (d, J = 2.7 Hz), 158.3 (d, J = 158.9 Hz), 160.0; ^{19}F NMR (376 MHz, $CDCl_3$): δ −110.8 (m).



Scheme 2.

*2.5.3. 2-Fluoro-4-methyl-2-penten-1-ol (**2b**)*

Product was separated by silica gel column chromatography (petroleum ether:ethyl acetate, 10:1) to afford a mixture of (*Z*)-**2b** and (*E*)-**2b** with a ratio of *E*:*Z* = 9:91, a pale yellow oil (2.8 g, 75% yield); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 50–120 °C, 0.5 °C/min. The retention time for (*E*)-**2b** was 10.373 min and for (*Z*)-**2b** was 12.057 min. ^{1}H NMR (400 MHz, $CDCl_3$): (*Z*)-isomer: δ 1.02 (d, J = 6.8 Hz, 6 H, $2CH_3$), 1.75 (br, 1H, OH), 2.76 (m, 1H, CH), 4.08 (d, J = 16.0 Hz, 2 H, CH_2), 4.70 (dd, J = 37.4 Hz and 9.6 Hz, 1H, CH); (*E*)-isomer: δ 1.02 (d, J = 6.8 Hz, 6 H, $2CH_3$), 1.75 (br, 1H, OH), 2.76 (m, 1H, CH), 4.24 (d, J = 21.2 Hz, 2H, CH_2), 5.06 (dd, J = 21.2 Hz and 10.4 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.8, 23.7 (d, J = 3.7 Hz), 61.5 (d, J = 32.40 Hz), 115.4 (d, J = 13.3 Hz), 155.9 (d, J = 251.50 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): (*Z*)-isomer: δ −123.40 (m); (*E*)-isomer: δ −118.55 (m).

*2.5.4. (Z)-2-Fluoro-2-hexen-1-ol (**2c**)*

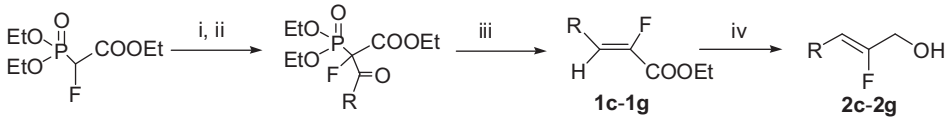
Purification by silica gel column chromatography (petroleum ether:ethyl acetate, 10:1) gave **2c** as a colorless oil (85%); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 50–120 °C, 2 °C/min. The retention time for **2c** was 11.832 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 7.2 Hz, 3H, CH_3), 1.40 (m, 2H, CH_2), 1.80 (br, 1H, OH), 2.09 (m, 2H, CH_2), 4.11 (d, J = 16.0 Hz, 2H, CH_2), 4.84 (dt, J = 36.8 Hz and J = 7.2 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 22.3 (d, J = 1.7 Hz), 25.4 (d, J = 4.0 Hz), 61.4 (d, J = 32.0 Hz), 108.0 (d, J = 14.0 Hz), 157.5 (d, J = 251.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.4 (m).

*2.5.5. (Z)-6-Chloro-2-fluoro-2-hexen-1-ol (**2d**)*

Purification by silica gel column chromatography (petroleum ether:ethyl acetate, 8:1) gave the product **2d** (80% yield); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 90–120 °C, 1 °C/min. The retention time for **2d** was 12.073 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.75 (br, 1H, OH), 1.86 (m, 2H, CH_2), 2.26 (m, 2H, CH_2), 3.53 (t, J = 6.8 Hz, 2H, CH_2Cl), 4.10 (d, J = 15.2 Hz, 2H, CH_2), 4.83 (dt, J = 36.8 Hz and J = 7.6 Hz, 1H, CHF); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.84 (d, J = 4.6 Hz), 31.98 (d, J = 1.9 Hz), 44.23, 61.24 (d, J = 32.5 Hz), 106.01 (d, J = 13.6 Hz), 158.46 (d, J = 253.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −119.5 (m).

*2.5.6. (Z)-2-Fluoro-2-octen-1-ol (**2e**)*

Purification by silica gel column chromatography (petroleum ether:ethyl acetate, 10:1) gave the product **2e** (80%); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 90–120 °C, 1 °C/min. The retention time for **2e** was 9.507 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 6.8 Hz, 3H, CH_3), 1.26–1.40 (m, 6H, $3CH_2$), 1.99 (br, 1H, OH), 2.09 (m, 2H, CH_2), 4.10 (d, J = 16.0 Hz, 2H, CH_2), 4.83 (dt, J = 36.8 Hz and J = 7.6 Hz, 1H, CHF); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.5, 23.3(d, J = 4.1 Hz), 28.9 (d, J = 1.5 Hz), 31.4, 61.4 (d, J = 32.3 Hz), 108.3 (d, J = 14.0 Hz), 157.4 (d, J = 251.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.5 (m).



c: R=$CH_3(CH_2)_2$ **e**: R=$CH_3(CH_2)_4$ **g**: R=$CH_3(CH_2)_{10}$
d: R=$Cl(CH_2)_3$ **f**: R=$CH_3(CH_2)_6$

Reagents and conditions: (i) n-BuLi, THF, -40 °C, 1 h; (ii) RCOCl, THF, -40 °C to rt, 4 h; (iii) $NaBH_4$, EtOH, -78 °C to rt; (iv) DIBAL, THF, 0 °C to rt, 4 h.

Scheme 3. Reagents and conditions: (i) n-BuLi, THF, −40 °C, 1 h; (ii) RCOCl, THF, −40 °C to rt, 4 h; (iii) $NaBH_4$, EtOH, −78 °C to rt; (iv) DIBAL, THF, 0 °C to rt, 4 h.

*2.5.7. (Z)-2-Fluoro-2-decen-1-ol (**2f**)*

Purification by silica gel column chromatography (petroleum ether:ethyl acetate, 10:1) gave the product **2f** (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H, CH_3), 1.25–1.41 (m, 10H, $5CH_2$), 1.75 (br, 1H, OH), 2.10 (m, 2H, CH_2), 4.10 (d, J = 16.0 Hz, 2H, CH_2), 4.83 (dt, J = 37.2 Hz and J = 7.6 Hz, 1H, CHF); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 23.3, 29.1 (d, J = 5.9 Hz), 29.7, 31.8, 61.5 (d, J = 32.4 Hz), 108.3 (d, J = 13.7 Hz), 157.4 (d, J = 251.9 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −122.8 (m).

*2.5.8. (Z)-2-Fluoro-2-tetradecen-1-ol (**2g**)*

Purification by silica gel column chromatography (petroleum ether:ethyl acetate, 10:1) gave the product **2g** (80%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J = 6.8 Hz, 3H, CH_3), 1.25–1.38 (m, 18H, $9CH_2$), 1.82 (br, 1H, OH), 2.11 (m, 2H, CH_2), 4.10 (d, J = 16.0 Hz, 2H, CH_2), 4.85 (dt, J = 36.8 Hz and 7.6 Hz, 1H, CHF); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 23.4 (d, J = 4.0 Hz), 29.2, 29.3, 29.4, 29.6, 29.6, 29.7, 31.9, 61.5 (d, J = 32.3 Hz), 108.3 (d, J = 14.0 Hz), 157.4 (d, J = 251.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −121.5 (m).

2.6. General procedure for the biotransformation with Baker's yeast

20 mL of sodium phosphate buffer (0.1 M) solution and 2.0 g of dry baker's yeast were added into a 100 mL Erlenmeyer flask. After shaking 15 min at 30 °C, 2-fluoroallylic alcohols **2** were added. The mixture was maintained at 30 °C in a shaker at 150 rpm. At the end of the reactions, the mixture was treated by a centrifuge at 3500 rpm/min for 30 min. The supernatant was extracted by ethyl acetate (3× 20 mL), dried over sodium sulfate and the solvent was evaporated. The residue was flashed on a short silica gel column using ethyl acetate as eluent (20 mL) and analyzed by GC to determine the conversion.

*2.6.1. 2-Fluoro-3-(4-methoxyphenyl)propanol (**3a**)*

$[\alpha]_D^{25} = -11.4°$ (c = 1, $CHCl_3$, 92% ee); enantiomeric excesses were determined by HPLC (Daicel Chiralpak AS-H, 0.5 mL/min, using 5% i-PrOH: 95% n-hexane, 276 nm, retention time: t_{major} = 67.232 min, and t_{minor} = 80.140 min). GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 160 °C. The retention time for **3a** was 11.05 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.02 (br, 1H, OH), 2.68–2.98 (m, 2H, CH_2), 3.62–3.79 (m, 2H, CH_2), 3.81 (s, 3H, OCH_3), 4.73 (ddq, J = 48.8 Hz, 2.4 Hz and 6.0 Hz, 1H, CHF), 6.85 (d, J = 8.8 Hz, 2H, Ar), 7.15 (d, J = 8.8 Hz, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.5 (d, J = 21.0 Hz), 55.3, 64.1 (d, J = 22.0 Hz), 94.8 (d, J = 181.0 Hz), 114.0, 128.3 (d, J = 6.0 Hz), 130.3, 158.5; ^{19}F NMR (376 MHz, $CDCl_3$): δ −187.6 (m).

*2.6.2. 2-Fluoro-4-methyl-1-pentanol (**3b**)*

$[\alpha]_D^{25} = -63.6°$ (c = 1, $CHCl_3$, 91% ee); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 50–120 °C, 0.5 °C/min. The retention time for **3b** was 11.098 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (d, J = 6.4 Hz, 6H, $2CH_3$), 1.21–1.36 (m, 1H, CH), 1.62–1.85 (m, 2H, CH_2), 3.60–3.76 (m, 2H, CH_2), 4.70 (m, 1H, CHF); ^{19}F NMR (376 MHz, $CDCl_3$): δ −190.1 (m).

*2.6.3. 2-Fluoro-1-hexanol (**3c**)*

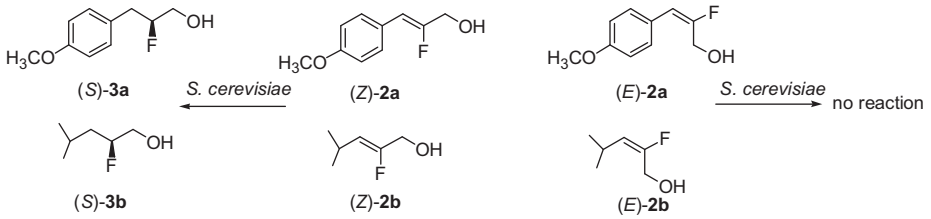
$[\alpha]_D^{25} = -5.28°$ (c = 1, $CHCl_3$, 78% ee); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 50–120 °C, 2 °C/min. The retention time for **3c** was 10.565 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (t, J = 6.8 Hz, 3H, CH_3), 1.34–1.71 (m, 6H, $3CH_2$), 3.62–3.78 (m, 2H, CH_2), 4.58 (m, 1H, CHF); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.5, 27.1 (d, J = 4.9 Hz), 30.7 (d, J = 20.2 Hz), 65.1 (d, J = 21.5 Hz), 94.8 (d, J = 166.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −189.5 (m).

*2.6.4. 6-Chloro-2-fluoro-1-hexanol (**3d**)*

$[\alpha]_D^{25} = -11.04°$ (c = 0.8, $CHCl_3$, 91% ee); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 90–120 °C, 1 °C/min. The retention time for **3d** was 11.182 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53–1.86 (m, 6H, $3CH_2$), 1.83 (br, 1H, OH), 3.55 (t, J = 6.8 Hz, 2H, CH_2), 3.63–3.79 (m, 2H, CH_2), 4.58 (m, 1H, CHF); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4 (d, J = 4.7 Hz), 30.2 (d, J = 20.6 Hz), 32.3, 44.7, 64.9 (d, J = 21.7 Hz), 94.4 (d, J = 167.3 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −190.0 (m).

*2.6.5. 2-Fluoro-1-octanol (**3e**)*

$[\alpha]_D^{25} = -7.55°$ (c = 0.4, $CHCl_3$, 92% ee); GC conditions: the column AT-SE-30 30 m × 0.25 mm, the carrier gas: N_2, the column temperature 90–120 °C, 1 °C/min. The retention time for **3e** was 8.740 min. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H, CH_3), 1.25–1.46 (m, 8H, $4CH_2$), 1.68 (m, 2H, CH_2), 3.62-–3.77 (m, 2H, CH_2), 4.48–4.66 (m, 1H, CHF); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.5, 24.9 (d, J = 4.8 Hz), 29.1, 31.0 (d, J = 20.1 Hz), 31.7, 65.1 (d, J = 21.6 Hz), 94.8 (d, J = 166.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$): δ −189.6 (m).



Scheme 4.

2.7. General procedure for preparing racemates **3**

A round-bottomed flask was charged with fluorinated allylic alcohols (100 mg), Pd/C (4 mol%) and methanol (abs, 10 mL). The mixture was stirred under hydrogen atmosphere (1 atm) for 2 h, and then was filtered through Buchner funnel with fritted disc and the solvent was removed under vacuo. Purification by silica gel column chromatography gave the racemic saturated alcohols **3**.

2.8. General procedure for preparing MTPA esters **4**

(*R*)-(+)-α-Methoxy-α-(trifluoromethyl)phenylacetic acid (0.65 mmol) was dissolved in 2 mL of dichloromethane. $SOCl_2$ (1.96 mmol) was added and then heat it to 75 °C, reflux for 1–2 h. Evaporation of the solvent, (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was formed. The above product **3** (0.5 mmol) was dissolved in 5 mL of dichloromethane. Triethylamine (0.55 mmol) and DMAP (0.03 mmol) were added. The reaction was cooled to 0 °C (ice bath) and (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride was added (0.65 mmol) dropwise. After addition the reaction was allowed to warm at room temperature for 12 h. Reaction mixture was diluted with 5 mL NH_4Cl (aq.) and poured into an extraction funnel, another 5 mL of CH_2Cl_2 and NH_4Cl (aq.) was added and the layer was separated. The aqueous layer was washed with CH_2Cl_2 (2× 5 mL) and dried over with sodium sulfate. The solvent was removed under vacuo.

2.8.1. MTPA ester of 2-fluoro-3-(4-methoxyphenyl)propanol (**4a**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.85–2.97 (m, 2H, CH_2), 3.57 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.25–4.54 (m, 2H, CH_2), 4.79–4.93 (m, 1H, CHF), 6.81 (d, *J* = 8.8 Hz, 2H, Ar), 7.03 (d, *J* = 8.8 Hz, 2H, Ar), 7.42 (m, 3H, Ar), 7.53 (m, 2H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.7 (s, CF_3), −184.7 (m, CHF, major), −185.3 (m, CHF, minor).

2.8.2. MTPA ester of 2-fluoro-4-methyl-1-pentanol (**4b**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (d, *J* = 5.6 Hz, 3H, CH_3), 0.94 (d, *J* = 5.6 Hz, 3H, CH_3), 1.28–1.37 (m, 1H, CH), 1.60–1.80 (m, 2H, CH_2), 3.57 (s, 3H, OCH_3), 4.32–4.49 (m, 2H, CH_2), 4.72–4.86 (m, 1H, CHF), 7.41 (m, 3H, Ar), 7.53 (m, 2H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.740 (s, CF_3, minor), −71.796 (s, CF_3, major), −187.5 (m, CHF).

2.8.3. MTPA ester of 2-fluoro-1-hexanol (**4c**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, *J* = 7.2 Hz, 3H, CH_3), 1.47–1.68 (m, 6H, $3CH_2$), 3.572 (s, 3H, OCH_3), 4.42 (m, 2H, CH_2), 4.70 (m, 1H, CHF), 7.41 (m, 3H, Ar), 7.53 (m, 2H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.763 (s, CF_3, minor), −71.814 (s, CF_3, major), −187.0 (m, CHF).

2.8.4. MTPA ester of 6-chloro-2-fluoro-1-hexanol (**4d**)

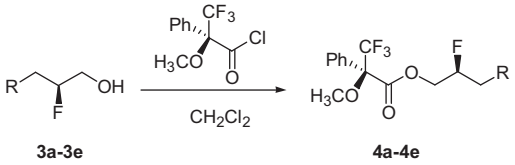
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53–1.80 (m, 6H, $3CH_2$), 3.52 (t, *J* = 6.8 Hz, 2H, CH_2), 3.57 (d, *J* = 0.8 Hz, 3H, OCH_3), 4.34–4.52 (m, 2H, CH_2), 4.64–4.81 (m, 1H, CHF), 7.42 (m, 3H, Ar), 7.53 (m, 2H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.725 (s, CF_3, minor), −71.749 (s, CF_3, major), −187.3 (m, CHF).

2.8.5. MTPA ester of 2-fluoro-1-octanol (**4e**)

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.2 Hz, 3H, CH_3), 1.27–1.70 (m, 10H, $5CH_2$), 3.57 (d, *J* = 0.2 Hz, 3H, OCH_3), 4.29–4.52 (m, 2H, CH_2), 4.63–4.78 (m, 1H, CHF), 7.41 (m, 3H, Ar), 7.53 (m, 2H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$): δ −71.750 (s, CF_3, minor), −71.804 (s, CF_3, major), −186.9 (m, CHF).

3. Results and discussion

(*Z*)-2-Fluoro-3-(4-methoxyphenyl)-2-propen-1-ol [(*Z*)-**2a**] and 2-fluoro-4-methyl-2-penten-1-ol (**2b**) were prepared by the direct condensation of ethyl fluoroacetate with the corresponding aldehydes and the subsequent reduction with DIBAL (Scheme 2). Stereoselective Horner–Wadsworth–Emmons (HWE) reaction of triethyl 2-fluoro-2-phosphonoacetate with *p*-methoxylbenzaldehyde was performed for preparing **1a** with a ratio of *E*:*Z* = 3:1 [24]. After reduction of **1a** (*E*:*Z* = 3:1) with DIBAL, pure (*E*)-**2a** was isolated by purification with silica gel column chromatography. (*Z*)-2-Fluoro-2-alken-1-ols (**2c–2g**) were synthesized by a tandem reduction-olefination of triethyl 2-acyl-2-fluoro-2-phosphonoacetates and the subsequent reduction with DIBAL [25,26] (Scheme 3).



3a-3e 4a-4e

Scheme 5.

Bioreduction was carried out by shaking a mixture of the substrate **2** and dry baker's yeast in sodium phosphate buffer solution (PBS) at 30 °C. The product yields were determined by GC and calculated based on the amount of the substrate **2** added. As reported previously, the (*E*/*Z*) configuration of the cinnamyl alcohol played a crucial role in the reduction mediated by baker's yeast [27]. In the present work, we become interested in the influence of configuration of 2-fluorinated allyl alcohols on the bioreduction. 2-Fluoroallylic alcohols (**2a–2b)** with different configurations were used as the substrates. Under the above conditions, we found that (*Z*)-**2a** was almost completely converted into (*S*)-**3a** with 92% ee within 48 h [23], whereas (*E*)-**2a** could not be reduced even the reaction time was prolonged to one week. In order to confirm this remarkable difference in reactivity of (*E*/*Z*) isomers, substrate with alkyl group at β position of C=C bond **[2b** (*E*:*Z* = 9:91)] was tested. As a consequence, only (*Z*)-**2b** could be readily reduced into 2-fluoro-4-methyl-1-pentanol (**3b**) with 91% ee by baker's yeast after 48 h, and (*E*)-**2b** was totally remained in the reaction mixture (Scheme 4). As known to us, the reduction mechanism for cinnamyl alcohols mediated by baker's yeast had been investigated in the earlier work [28]. It is shown that alcohol dehydrogenase from baker's yeast has specificity with respect to *E* versus *Z* configuration, and neither the corresponding aldehyde nor the saturated alcohols could be formed from (*Z*)-isomer of cinnamyl alcohols. Apparently, the reason for no reaction of (*E*)-**2a** and (*E*)-**2b** in our experiments is also followed this observation, because replacement of the hydrogen atom by a fluorine atom at 2-position of (*Z*)-allyl alcohols leads to the formation of (*E*)-2-fluorinated allyl alcohols. Hence, all of the substrates with *Z* configuration were used in the following reduction reactions. The absolute configuration of the new compound **3b** was assigned to be *S* by determining its optical rotation degree and characterizing the structure of its Mosher ester (Scheme 5). The changes in chemical shifts of the $-CF_3$ for ^{19}F NMR were typical for the stereomers of the Mosher esters: δ −71.74 and −71.79 (CF_3, s) for the Mosher ester of racemic **3b**, −71.79 for the Mosher ester of (*S*)-**3b**.

Next, we focused our attention on the effect of the alkyl chain length of R group on the reduction of 2-fluoro-2-alken-1-ols. As shown in Table 1, 2-fluoro-2-hexen-1-ol (**2c**) was consumed completely within 48 h, giving the product **3c** almost quantitatively with 78% ee (entry 1). When R group was changed to 3-chloropropyl group, compound **3d** was readily yielded with 91% ee from bioreduction of substrate **2d** (entry 2). The facile formation of **3d** enables us to prepare some useful derivatives like fluorinated diol or amino alcohol by replacing the chlorine atom of **3d** with various nucleophiles. Under the same reaction conditions, only 75% of **2e** was converted into saturated alcohol **3e** due to the low conversion

Table 1
Effect of the alkyl group and concentration of the substrate on baker's yeast mediated bioreduction[a].

Entry	**2** (loading)	Product	Yield (%)	Ee (%)	$[\alpha]_D^{25}(CHCl_3)$
1[b]	**2c** (40 mg)	**3c**	99	78	−5.28°(*c* 1.0)
2[b]	**2d** (40 mg)	**3d**	99	91	−11.04°(*c* 0.8)
3[b]	**2e** (40 mg)	**3e**	75	nd	nd
4[b]	**2e** (30 mg)	**3e**	99	92	−7.55°(*c* 0.4)
5[b]	**2e** (20 mg)	**3e**	99	92	−7.55°(*c* 0.4)
6[c]	**2f** (40 mg)	**3f**	46	nd	nd
7[c]	**2g** (40 mg)	**3g**	0	nd	nd

[a] BY (2.0 g), pH 7.0 PBS (20 mL), 30 °C, 48 h, 0.1 mL of *n*-butanol (5.5×10^{-5} mol L^{-1}) was added.
[b] Yield determined by GC, ee% value by ^{19}F NMR analysis of their MTPA esters.
[c] Yield determined by ^{1}H NMR.

rate (entry 3). However, the yield of **3e** was raised to 99% when the amount of **2e** was reduced from 40 mg to 30 mg (entry 5). Obviously, the substrate concentration has a marked effect on the conversion of bioreduction. When the alkyl chain increased to heptyl group, the yield of **3f** was sharply reduced to 46% (entry 6). It was hardly to be reduced when the substrate **2g** with a much longer alkyl group (R=*n*–$C_{11}H_{23}$) was used (entry 7). These results clearly indicate that the length of R group strongly affects the reaction rate. With the increase of the length of alkyl group at β position of C=C bond, the conversion rate declined obviously. The probable reason for moderate ee value of **3c** might be the small size of n-propyl group at β position of C=C bond. In fact, there is a relationship between the enantioselectivity of reduction and the difference in size of substituents attached to C=O bond of ketones [29]. And for the reduction of conjugated enals, the substituents at β position of C=C bond should be one group is large and the other small [4]. In addition, the absolute configuration of **3c** and **3e** were determined to be *S* by comparing their optical rotations with the literature data [30,31]. And the configuration of new compound **3d** was also assigned to be *S*. Left rotation was observed both for **3b** and **3d** as did for **3c** and **3e**. The analysis of ^{19}F NMR spectra data of the Mosher eaters for the optically active compounds **3b**–**3d** and **3e** and their corresponding racemates clearly indicated that the configurations of **3b** and **3d** were the same to that of **3c** and **3e**. The changes in chemical shifts of the $-CF_3$ for ^{19}F NMR for these Mosher esters were given as follows: δ −71.76 and −71.81 (CF_3, s) for Mosher ester of racemic **3c**, −71.81 for Mosher ester of (*S*)-**3c**; δ: −71.72 and −71.75 (CF_3, s) for Mosher ester of racemic **3d**, −71.75 for Mosher ester of (*S*)-**3d**; δ: −71.76 and −71.81 (CF_3, s) for Mosher ester of racemic **3e**, −71.81 for Mosher ester of (*S*)-**3e**.

The catalytic mechanism of the enzymatic reduction of activated olefins catalyzed by enoate reductases has been studied in great detail [32–34], and it has shown that a hydride from the reduced cofactor is stereoselectively transferred to β-carbon respect to the activating group, whereas a Tyr residue adds a proton (which is ultimately derived from the solvent) to α-carbon from the opposite side [4]. The bioreduction of 2-fluorinated allyl alcohol here investigated involves the addition of a hydrogen atom to β-carbon respect to the activating group from the upper part of its enal generated *in situ* by dehydrogenation, while α-protonation takes place in *anti* manner, and finally yields (*S*)-products [34].

The effect of the amount of baker's yeast and the pH value of phosphate buffer solution was also estimated. As shown in Table 2, when the amount of baker's yeast was reduced from 2.0 g to 1.5 g, **2e** could also be quantitatively converted into the product **3e** (entry 1). But a decline in conversion appeared when the amount of baker's yeast was decreased to 1.0 g (entry 2). Only 15% of **3e** was detected by using 0.5 g baker's yeast for bioreduction (entry 3). Another interesting result was observed by changing pH value of the phosphate buffer solution. The conversion rate for **2e** was somewhat dependent on the pH value, and relatively low conversions were observed in the pH 6.5 and pH 7.5 phosphate buffer solutions (entry 4 and 5). The effect of the pH value and the amount of baker's yeast on enantioselectivity was not studied carefully because our recent result showed these two factors just had a little influence [15].

Table 2
Effect of pH and amount of baker's yeast on bioreduction of 2e[a].

Entry	BY (g)	pH	Product	Yield (%)[b]
1	1.5	7.0	**3e**	99
2	1.0	7.0	**3e**	80
3	0.5	7.0	**3e**	15
4	1.5	6.5	**3e**	85
5	1.5	7.5	**3e**	78

[a] **2e** (30 mg), PBS (20 mL), 30 °C, 48 h, 0.1 mL of *n*-butanol (5.5×10^{-5} mol L^{-1}) was added.
[b] Determined by GC.

4. Conclusion

In conclusion, the baker's yeast mediated bioreduction of 2-fluoro-2-alken-1-ols led to the formation of chiral 2-fluorinated primary alcohols with high stereoselectivity. The configuration of the substrates had a crucial effect on the reduction, only (*Z*)-isomers rather than (*E*)-isomers could be readily reduced by baker's yeast. Moreover, the reactivity of the substrate was also dependent upon the chain length of the alkyl group at β position, and a sharp decline in reactivity was observed when the alkyl chain increased to C_7H_{15}. Reaction conditions involving the concentration of substrate, the pH value of PBS and the amount of baker's yeast also had an important effect on reaction rate of 2-fluoroallylic alcohols.

Acknowledgments

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