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Asymmetric Reductions of (Trifluoroacetyl)biphenyl Derivatives with Bakers' Yeast and with *Geotrichum candidum* Acetone Powder

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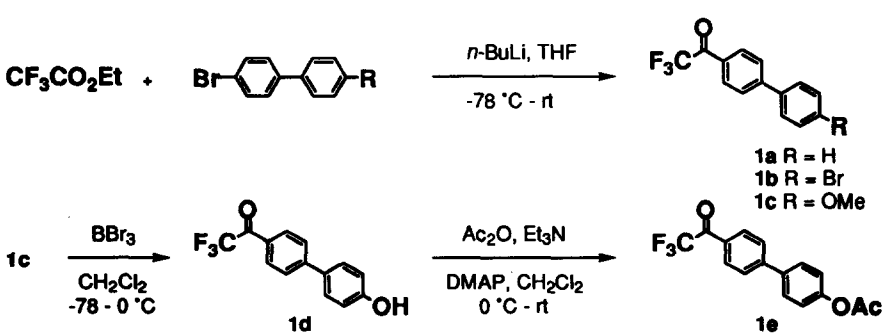
Abstract : The bakers' yeast reduction of (trifluoroacetyl)biphenyl derivatives produces (*R*)-trifluoromethyl biphenylyl carbinols in high enantioselectivity, whereas the reduction of the same derivatives with *Geotrichum candidum* acetone powder gives the corresponding (*S*)-carbinols in excellent yields and enantioselectivity.

Microbial reduction has been widely used for the synthesis of chiral alcohols.[1] Fluorine-containing optically active alcohols are of great value due to their potential use as ferroelectric liquid crystals,[2] drugs,[3] and tools for metabolic studies.[4] Enantiomers of chiral trifluoromethyl carbinols are usually obtained by resolution of the racemates[5] involving kinetic resolution by lipases,[6] by asymmetric reduction of the corresponding trifluoromethyl ketones with chiral chemical reagents,[7] or bakers' yeast.[8] Generally, the bakers' yeast reduction does not always produce a trifluoromethyl carbinol with high enantioselectivity due to the substrate specificity encountered, which consequently should be overcome by modification of the substrate, and/or other microbial reductions should be screened to circumvent such problems.[9] For example reductions of trifluoroacetophenone and trifluoroacetonaphthalene with baker's yeast do not meet with satisfactory enantiofacial discrimination, and the optical purities of the reduced alcohols are 44% and 66% ee, respectively.[10] Recently, stereochemical control of microbial reduction to obtain an optically active alcohol of the desired configuration has been achieved using organic solvents,[11,12] additives,[13] or inhibitors of unnecessary enzyme(s).[14] Asymmetric reduction of ketones by *Geotrichum candidum* acetone powder was also reported.[15] We have already reported the preparation of optically active trifluoromethylbenzyl alcohols possessing *p*-substituents by the bakers' yeast reduction,[16] which offers a good access for the construction of ferroelectric liquid crystals. In this paper, we would like to report asymmetric reductions of (trifluoroacetyl)biphenyl derivatives with bakers' yeast and with *Geotrichum candidum* acetone powder to give (*R*) and (*S*)-alcohols, respectively.

The starting materials of 4-(trifluoroacetyl)biphenyl **1a**, 4-bromo-4'-(trifluoroacetyl)biphenyl **1b**, and 4-methoxy-4'-(trifluoroacetyl)biphenyl **1c** were prepared by trifluoroacetylation of 4-bromobiphenyl



derivatives with ethyl trifluoroacetate. The phenol derivative **1d** was prepared by demethylation of 4-methoxy-4'-(trifluoroacetyl)biphenyl **1c** with boron tribromide. Further protection of the hydroxy group in **1d** with the

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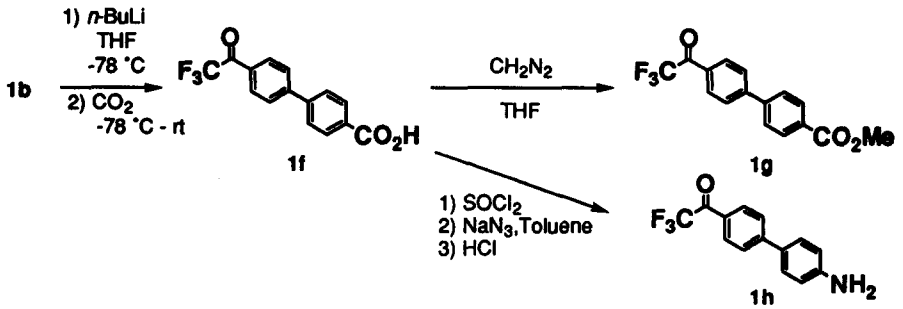
acetyl group gave the acetate **1e**. 4-[4'-(Trifluoroacetyl)phenyl]benzoic acid **1f** was prepared by carboxylation of **1b**, which upon methyl esterification afforded methyl 4-[4'-(trifluoroacetyl)phenyl]benzoate **1g**. 4-Amino-4'-(trifluoroacetyl)biphenyl **1h** was also readily prepared from 4-[4'-(trifluoroacetyl)phenyl]benzoic acid **1f** by the Curtius rearrangement after conversion into the acyl azide via the acid chloride.



The bakers' yeast reduction was carried out according to the general procedure to give (*R*)-alcohols in good to excellent enantiomeric excess by modification of the *para*-substituent of the (trifluoroacetyl)biphenyl derivative. The results are summarized in Table 1.

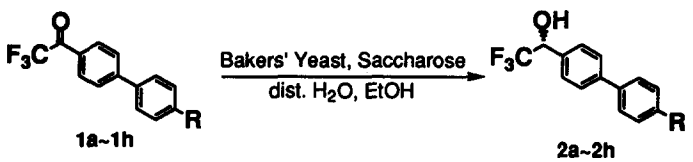


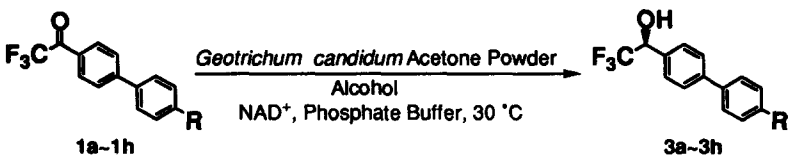
Table 1. Reduction of (trifluoroacetyl)biphenyl derivatives by bakers' yeast.

entry	Compound	R	Saccharose [a]	Time (day)	Yield (%)[b]	% ee[c]	Config.
1	**1a**	H	+	4	74	96[d]	*R*
2	**1a**	H	-	2	34	93	*R*
3	**1b**	Br	+	3	30	78	*R*
4	**1b**	Br	-	6	30	74	*R*
5	**1c**	OMe	+	2	27	94[d]	*R*
6	**1c**	OMe	-	3	33	98	*R*
7	**1d**	OH	+	4	27	52	*R*
8	**1d**	OH	-	4	67	60	*R*
9	**1f**	CO_2H	+	5	12[e]	69	*R*
10	**1f**	CO_2H	-	10	23[e]	67	*R*
11	**1g**	CO_2Me	+	3	62	89	*R*
12	**1g**	CO_2Me	-	3	60	88	*R*
13	**1h**	NH_2	+	14	20	69	*R*
14	**1h**	NH_2	-	7	14	74	*R*

a) The marks of + or - represent in the presence or in the absence of saccharose, respectively. b) Isolated on preparative TLC. c) Determined by HPLC (Hibar RT 240) analysis of the corresponding (*R*)-MTPA esters. d) The enantiomeric excess of the products was determined by HPLC using a chiral stationary column (Dicel OJ). e) Isolated after methyl esterification with CH_2N_2

The bakers' yeast reduction of biphenyl derivative **1a** in the presence of saccharose as a hydride donor showed high enantiofacial discrimination to give the corresponding alcohol **2a** in good yield (entry 1). 4-Bromo-4'-(trifluoroacetyl)biphenyl **1b** showed moderate enantiofacial discrimination in the presence of saccharose (entry 3). The biphenyl derivative **1d** with a hydroxy group afforded the corresponding alcohol **2d** with moderate enantioselectivity (entry 7, 8), whereas enantioselectivity was improved by switching the alcohol to the methoxy group (entry 5, 6). However, the reduction of 4-acetoxy-4'-(trifluoroacetyl)biphenyl **1e** with bakers' yeast did not give alcohol **2e** even after 9 days, and the starting material was recovered in 25%. 4-[4'-(Trifluoroacetyl)phenyl]benzoic acid **1f** afforded the corresponding alcohol **2f** with moderate enantioselectivity (entry 9, 10). The methoxycarbonyl-substituted biphenyl derivative **1g** produced the optically active alcohol **2g** with 88% ee, and the reduction in the presence of saccharose improved the enantiomeric excess (entry 11). The amino derivative **1h** was reduced in the absence of saccharose to give the corresponding alcohol **2h** with moderate selectivity (entry 13, 14).

On the other hand, reduction of (trifluoroacetyl)biphenyl derivatives **1a~1h** with *Geotrichum candidum* acetone powder[15a] produced (*S*)-trifluoromethyl biphenylyl carbinols **3a~3h** in excellent yields and enantioselectivity with the opposite configuration to the products by bakers' yeast reduction. The results are summarized in Table 2.



1a~1h **3a~3h**

Table 2. Reduction of (trifluoroacetyl)biphenyl derivatives by *Geotrichum candidum* acetone powder.

entry	Compound	R	acetone powder (mg)	Alcohol	Time (h)	Yield (%)[a]	% ee[b]	Config.
1	**1a**	H	20	2-octanol	73	78	99	*S*
2	**1a**	H	60	2-octanol	73	81	98	*S*
3	**1b**	Br	20	2-octanol	73	40	98	*S*
4	**1b**	Br	60	2-octanol	73	61	96	*S*
5	**1c**	OMe	20	2-propanol	73	50	94[c]	*S*
6	**1c**	OMe	40	2-propanol	73	62	94	*S*
7	**1c**	OMe	60	2-octanol	73	74	98	*S*
8	**1d**	OH	20	2-propanol	16	84	98	*S*
9	**1e**	OAc	60	2-octanol	73	53	98	*S*
10	**1f**	CO_2H	60	2-octanol	90	21[d]	98	*S*
11	**1g**	CO_2Me	20	2-octanol	73	50	96	*S*
12	**1g**	CO_2Me	60	2-octanol	73	65	98	*S*
13	**1h**	NH_2	20	2-octanol	25	60	94	*S*
14	**1h**	NH_2	60	2-octanol	25	87	96	*S*

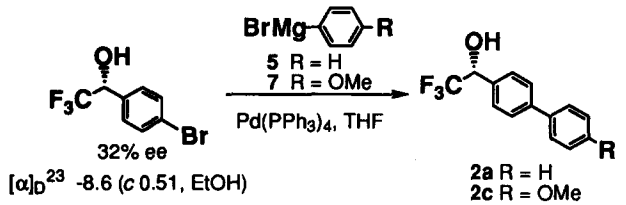
a) Isolated on preparative TLC. b) Determined by HPLC (Hibar RT 240) analysis of the corresponding (*R*)-MTPA esters. c) The enantiomeric excess of the products was determined by HPLC using a chiral stationary column (Dicel OJ). d) Isolated after methyl esterification with CH_2N_2

In the initial examination, when 4-(trifluoroacetyl)biphenyl **1a** was reduced by *Geotrichum candidum* acetone powder in the presence of 2-octanol as a reducing reagent of coenzyme (NAD^+), the corresponding alcohol **3a** with 99% ee was obtained in 78% yield, and the use of an increased amount of *Geotrichum candidum* acetone powder (x 3) recorded the increased yield up to 81% (entry 2). When 4-bromo-4'-

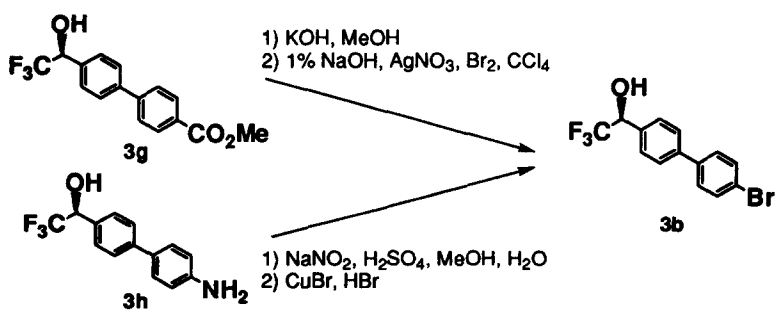
(trifluoroacetyl)biphenyl **1b** was reduced in the presence of 2-octanol as a reducing reagent, the alcohol **3b** with 98% ee was obtained in 40% yield (entry 3), and the use of an increased amount of *Geotrichum candidum* acetone powder (x 3) recorded the yield up to 61% (entry 4). 4-Methoxy-4'-(trifluoroacetyl)biphenyl **1c** afforded (*S*)-2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol **3c** with 94% ee using 2-propanol as a reducing reagent (entry 5). The use of 2-octanol improved both the enantiomeric excess and the yield of alcohol **3c** with 98% ee in 74% yield (entry 7). 4-Hydroxy-4'-(trifluoroacetyl)biphenyl **1d** afforded the alcohol **3d** with 98% ee in 84% yield in a short reaction time (entry 8). Although the bakers' yeast reduction of 4-acetoxy-4'-(trifluoroacetyl)biphenyl **1e** could not produce the alcohol **2e**, (*S*)-2,2,2-trifluoro-1-(4-acetoxy-4'-biphenylyl)ethanol **3e** with 98% ee was obtained in 53% yield using *Geotrichum candidum* acetone powder, making a distinct contrast each other (entry 9). The reduction of 4-[4'-(trifluoroacetyl)phenyl]benzoic acid **1f** afforded the alcohol **3f** in low yield (entry 10). Methyl 4-[4'-(trifluoroacetyl)phenyl]benzoate **1g** also afforded the alcohol **3g** with 98% ee in 65% yield using 2-octanol (entry 12). The amino derivative **1h** afforded the alcohol **3h** in good yield for a short reaction time (entry 13, 14).

It should be noted that bakers' yeast reduction gave (*R*)-trifluoromethyl biphenylyl cabinols **2** (Table 1), whereas (*S*)-trifluoromethyl biphenylyl cabinols **3** were produced by the reduction with *Geotrichum candidum* acetone powder (Table 2). These two microbial reductions compensate each other to give the optically active alcohols of desired configuration. Furthermore, a single recrystallization of the products afforded 100% enantiomerically pure carbinols.

The absolute configuration of (*S*)-2,2,2-trifluoro-1-(4-biphenylyl)ethanol **3a** was determined by the comparison with an authentic sample prepared as follows; the coupling reaction of the known (*R*)-2,2,2-trifluoro-1-(4'-bromophenyl)ethanol prepared from the bakers' yeast reduction[16] and the Grignard



reagent **5** in the presence of $Pd(PPh_3)_4$ gave (*R*)-2,2,2-trifluoro-1-(4'-biphenylyl)ethanol **2a**. A similar coupling with the Grignard reagent **7** gave (*R*)-2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol **2c**. (*S*)-2,2,2-Trifluoro-1-(4-hydroxy-4'-biphenylyl)ethanol **3d** was transformed into **3c** by methylation with



KHMDS and MeI. (*S*)-2,2,2-Trifluoro-1-(4-acetoxy-4'-biphenylyl)ethanol **3e** was also transformed into **3d** by deacetylation with sat. $NaHCO_3$ aq. in MeOH. The absolute configuration of (*S*)-2,2,2-trifluoro-1-(4-bromo-4'-biphenylyl)ethanol **3b** was also transformed into **3a** by reduction with *n*-BuLi. (*S*)-Trifluoromethyl carbinols **3g** and **3h** were also transformed into **3b**. Comparison of the sign of the optical rotation and/or the HPLC analysis using a chiral stationary column established the absolute configurations of all optically active alcohols prepared by the reduction of *Geotrichum candidum* acetone powder to be *S* and those by the bakers' yeast reduction to be *R*.

In conclusion, these microbial reductions were useful procedures to give optically active alcohols of desired configuration, where highly stereoselective reduction of (trifluoroacetyl)biphenyl derivatives by *Geotrichum candidum* acetone powder was accomplished to produce (*S*)-trifluoromethyl biphenylyl carbinols of the opposite configuration of the products by the bakers' yeast reduction with high enantioselectivity.

Experimental section

The dry bakers' yeast of S. I. Lesaffre was used in this experiment. *Geotrichum candidum* acetone powder IFO4597 was provided from Prof. Kaoru Nakamura of Kyoto University. Infrared spectra were determined on a JASCO IR-810 spectrometer. ^1H NMR spectra were recorded with JEOL α-500, JNM EX-270 spectrometer using tetramethylsilane as an internal standard. ^{19}F NMR spectra were recorded with Hitachi R-24F spectrometer using fluorotrichloromethane as an internal standard. High performance liquid chromatography (HPLC) was carried out on a Hitachi L-4000 detector and a Hitachi L-6000 pump using a Daicel Chiralcel OJ column. Optical rotations were measured with a Union PM-101 polarimeter. Exact mass spectra were taken on a JEOL JMS-DX303-HF spectrometer. All the melting points are uncorrected. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl immediately before use. Dichloromethane was pretreated with diphosphorus pentaoxide, distilled from CaH_2, and stored over molecular sieves 4A. Triethylamine was distilled from CaH_2. Methanol was distilled from magnesium methoxide and stored over molecular sieves 3A. Purification of products was performed by column chromatography on silica gel of Wako gel C-300, or Merck Silica Gel-60, and/or preparative TLC on silica gel of Merck Kieselgel 60 GF_{254} or Wako gel B-5F.

4-(Trifluoroacetyl)biphenyl 1a: To a solution of 4-bromobiphenyl (2.0 g, 8.58 mmol) in THF (33 ml) and Et_2O (10 ml) was added dropwise a solution of *n*-BuLi (4.3 ml, 8.58 mmol, 1.99 *N* in a hexane solution) at -45 °C. After 1 h stirring, a solution of ethyl trifluoroacetate (1.3 g, 9.4 mmol) in THF (5 ml) was added dropwise at -45 °C for 10 min, and the resulting mixture was stirred for 20 h. The reaction was quenched by aq. NaCl. After extraction of the entire mixture with ethyl acetate (10 ml x 3), the combined extracts were dried with Na_2SO_4, and the solvent was removed. The title compound was obtained by column chromatography on silica gel (1.5 g, 50%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, d, *J* = 7.33, 7.33 Hz, 1H), 7.45 (d, d, *J* = 7.33, 7.33 Hz, 1H), 7.51 (d, d, *J* = 7.33, 7.33 Hz, 1H), 7.65 (d, *J* = 7.33 Hz, 2H), 7.77 (d, *J* = 7.93 Hz, 2H), 8.16 (d, *J* = 7.93 Hz, 2H). ^{19}F NMR: δ -72.5 (s). IR ($CHCl_3$): 3100, 1710, 1610, 1350, 1160, 950 cm^{-1}. mp 49~50 °C. HRMS (EI^+): calcd for $C_{14}H_9OF_3$ (M^+), 280.0711. found: 280.0680.

4-Bromo-4'-(trifluoroacetyl)biphenyl 1b: The reaction was carried out as in the case with **1a** to give **1b** in 63% yield. ^1H NMR (270 MHz, $CDCl_3$): δ 7.51 (d, *J* = 8.58 Hz, 2H), 7.63 (d, *J* = 8.58 Hz, 2H), 7.73 (d, *J* = 8.58 Hz, 2H), 8.15 (d, *J* = 8.58 Hz, 2H). ^{19}F NMR: δ -73.0 (s). IR (KBr): 1710, 1600, 1180, 950 cm^{-1}. mp 75~77 °C. HRMS (EI^+): calcd for $C_{14}H_8OF_3Br$ (M^+), 327.9711. found: 327.9709.

4-Methoxy-4'-(trifluoroacetyl)biphenyl 1c: The reaction was carried out as in the case with **1a** to give **1c** in 47% yield. ^1H NMR (270 MHz, $CDCl_3$): δ 3.88 (s, 3H), 7.01 (d, *J* = 8.91 Hz, 2H), 7.60 (d, *J* = 8.91 Hz, 2H), 7.62 (d, *J* = 8.91 Hz, 2H), 8.13 (d, *J* = 8.91 Hz, 2H). ^{19}F NMR: δ -72.5 (s). IR ($CHCl_3$): 1715, 1600, 1300, 1150, 940 cm^{-1}. mp 111~113 °C. HRMS (EI^+): calcd for $C_{15}H_{11}O_2F_3$ (M^+), 280.0711. found: 280.0680.

4-Hydroxyl-4'-(trifluoroacetyl)biphenyl 1d: To a solution of **1c** (1 g, 3.57 mmol) in CH_2Cl_2 (10 ml) was added dropwise a solution of BBr_3 (6.06 ml, 6.06 mmol of a 1*M* dichloromethane solution) at -78 °C for 19 h. The reaction was quenched by aq. NaCl, and neutralized with $NaHCO_3$. The entire mixture was extracted with ethyl acetate (10 ml x 3), dried with Na_2SO_4, and the solvent was removed. The title compound was obtained by column chromatography on silica gel (671.4 mg, 71%). ^1H NMR (270 MHz, $CDCl_3$): δ 5.04 (s, 1H), 6.96 (d, *J* = 8.91 Hz, 2H), 7.55 (d, *J* = 8.91 Hz, 2H), 7.63 (d, *J* = 8.57 Hz, 2H), 8.12 (d, *J* = 8.57 Hz, 2H). ^{19}F NMR: δ -72.8 (s). IR ($CHCl_3$) : 3800, 3300, 1720, 1600, 1340, 1145, 940, 590, 525 cm^{-1}. mp 132~134 °C. HRMS (EI^+): calcd for $C_{14}H_9O_2F_3$ (M^+), 266.0555. found: 266.0550.

4-Acetoxy-4'-(trifluoroacetyl)biphenyl 1e: To a solution of **1d** (180 mg, 0.68 mmol), a catalytic amount of 4-dimethylaminopyridine (8.3 mg, 0.07 mmol), and triethylamine (140 μl, 1.01 mmol) in CH_2Cl_2 (5 ml) was added dropwise acetic anhydride (95.7 μl, 1.01 mmol) at 0 °C. After 8 h stirring, the reaction was quenched by aq. NaCl. The entire mixture was extracted with ethyl acetate (5 ml x 3). The combined extracts were dried with Na_2SO_4, and the solvent was removed. The title compound was obtained by column chromatography on silica gel (180.0 mg, 86%). ^1H NMR (270 MHz, $CDCl_3$): δ 2.33 (s, 3H), 7.23 (d, *J* = 8.57 Hz, 2H), 7.65 (d, *J* = 8.90 Hz, 2H), 7.73 (d, *J* = 8.90 Hz, 2H), 8.14 (d, *J* = 8.90 Hz, 2H). ^{19}F NMR: δ -69.5 (s). IR ($CHCl_3$): 1760, 1730, 1370, 1280, 1140, 1000, 980, 910 cm^{-1}. mp 115~117 °C. HRMS (EI^+): calcd for $C_{16}H_{11}O_3F_3$ (M^+), 308.0660. found: 308.0663.

4-[4'-(Trifluoroacetyl)biphenyl]benzoic acid 1f: 4,4'-Dibromobiphenyl (4 g, 12.8 mmol), *n*-BuLi (10.12 ml, 16.7 mmol, 1.65 *N* in a hexane solution), and ethyl trifluoroacetate (1.82 g, 12.8 mmol) were used as in the case with **1a**. To the resulting mixture prepared from 4,4'-dibromobiphenyl and ethyl trifluoroacetate was added dropwise a solution of *n*-BuLi (10.12 ml, 16.7 mmol, 1.65 *N* in a hexane solution) at -78 °C. After 1 h stirring, to the mixture was added dry ice (1.7 g, 38.4 mmol). After 10 h stirring, the reaction was quenched by aq. NaCl. The entire mixture was extracted with ethyl acetate (10 ml x 3). The combined extracts were dried with Na_2SO_4, and the solvent was removed. The title compound was obtained by column chromatography on silica gel (2.9 g, 77%). ^1H NMR (270 MHz, $CDCl_3$ and CD_3OD): δ 7.71 (d, *J* = 8.25 Hz, 2H), 7.73 (d, *J* = 8.25 Hz, 2H), 7.79 (d, *J* = 8.57 Hz, 2H), 8.18 (d, *J* = 8.57 Hz, 2H). ^{19}F NMR: δ -73.0 (s). IR ($CHCl_3$): 3075, 1680, 1600, 1420, 1300, 1180, 1140, 940, 840, 760, 670, 560, 520 cm^{-1}. mp 208~210 °C. HRMS (EI^+): calcd for $C_{15}H_9O_2F_3$ (M^+), 290.0504. found: 294.0458.

Methyl 4-[4'-(trifluoroacetyl)phenyl]benzoate 1g: To a solution of **1f** (418.0 mg, 1.42 mmol) in Et_2O (5 ml) was added dropwise a solution of CH_2N_2 at room temperature. The mixture was concentrated to give a crude product. The title compound was obtained by column chromatography on silica gel (183 mg, 42%). ^1H NMR (270 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.71 (d, *J* = 7.92 Hz, 2H), 7.79 (d, *J* = 8.25 Hz, 2H), 8.15 (d, *J* = 8.25 Hz, 2H), 8.17 (d, *J* = 7.92 Hz, 2H). ^{19}F NMR: δ -72.5 (s). IR ($CHCl_3$): 1720, 1610, 1360, 1300, 1160, 1110, 940 cm^{-1}. mp 92~94 °C. HRMS (EI^+): calcd for $C_{16}H_{11}O_3F_3$ (M^+), 308.0660. found: 308.0698.

4-Amino-4'-(trifluoroacetyl)biphenyl 1h: To **1f** (696 mg, 2.37 mmol) was added thionyl chloride (205.6 mmol, 15 ml) at 80 °C. After 12 h stirring at the same temperature, the solvent was removed in vacuo. To the residue was added toluene solution (15 ml) of NaN_3 (231 mg, 3.56 mmol). The mixture was stirred for 23 h at refluxing temperature. The mixture was then filtered, and to the filtrate was added conc. HCl (2.53 ml). The mixture was stirred for 2 h at 100 °C, and neutralized with aq. NH_3. The entire mixture was extracted with CH_2Cl_2 (10 ml x 3). The combined extracts were dried with Na_2SO_4, and the solvent was removed. The title compound was obtained by column chromatography on silica gel (377.2 mg, 60%). ^1H NMR (270 MHz, $CDCl_3$): δ 3.88 (br, 2H), 6.77 (d, *J* = 8.24 Hz, 2H), 7.50 (d, *J* = 8.58 Hz, 2H), 7.70 (d, *J* = 8.58 Hz, 2H), 8.09 (d, *J* = 8.24 Hz, 2H). ^{19}F NMR: δ -73.0 (s). IR (KBr): 3500, 3400, 1720, 1640, 1600, 1180, 980 cm^{-1}. mp 124~126 °C. HRMS (EI^+): calcd for $C_{14}H_{10}ONF_3$ (M^+), 265.0714. found: 265.0737.

A typical procedure of bakers' yeast reduction: Dry bakers' yeast (S. I. Lesaffre, 1.8 g), saccharose (Wako, 2.2 g) and dist. H_2O were mixed and stirred vigorously at room temperature for 60 min.

In the case where no saccharose was used, dry bakers' yeast (2.2 g) was simply stirred with dist. H_2O until homogeneous. Then 4-methoxy-4'-(trifluoroacetyl)biphenyl **1c** (101 mg, 0.36 mmol) dissolved in 2 ml of ethanol was added to the broth with constant stirring. Standard work-up followed by silica gel thin layer chromatography allowed the isolation of (*R*)-2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol **2c** (34 mg, 0.12 mmol, 33%, 98% ee) as a white crystal. The ratio of the enantiomers was determined by HPLC (*n*-C_6H_{14} : *i*-PrOH = 2 : 1) using a chiral stationary column (Daicel OJ) to be *R* : *S* = 99 : 1 (retention time; 44 min : 60 min, flow 0.5 ml / min).

A typical procedure of the reduction with *Geotrichum candidum* acetone powder: 4-Methoxy-4'-(trifluoroacetyl)biphenyl **1c** (25 mg, 0.08 mmol), 2-propanol (50 μl), NAD^+ (4 mg) and *Geotrichum candidum* acetone powder IFO4597 (20 mg) were added to 3 ml of phosphate buffer (Na_2HPO_4-KH_2PO_4, pH 7.0). The mixture was stirred at 30 °C for 73 h, and filtered through a celite pad. The entire mixture was extracted with ethyl acetate. The combined extracts were concentrated under reduced pressure to give a crude compound. The crude product was purified on preparative TLC to afford (*S*)-2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol **3c** (11.3 mg, 0.04 mmol, 50%, 94% ee) as a white crystal. The ratio of the enantiomers was determined by HPLC (*n*-C_6H_{14} : *i*-PrOH = 2 : 1) using a chiral stationary column (Daicel OJ) to be *R* : *S* = 3 : 97, 94% ee (retention time; 44 min : 60 min, flow 0.5 ml / min).

Enantiomerically enriched 2,2,2-trifluoro-1-biphenylylethanol: ^1H NMR (270 MHz, $CDCl_3$): δ 2.66 (d, *J* = 4.62 Hz, 1H), 5.08 (d, q, *J* = 4.62, 6.60 Hz, 1H), 7.34-7.65 (m, 9H). ^{19}F NMR: δ -80.0 (d, *J* = 6.60 Hz). IR ($CHCl_3$): 3600, 3300, 1610, 1500, 1360, 1300, 1140, 600 cm^{-1}. *R* form mp 122~124 °C. *S* form mp 124~125 °C (from *n*-hexane). HRMS (EI^+): calcd for $C_{14}H_{11}OF_3$ (M^+), 252.0762. found: 252.0731. *R* form, **2a** $[\alpha]_D^{23}$ -28.5 (*c* 0.99, $CHCl_3$), 96% ee; *S* form, **3a** $[\alpha]_D^{23}$ +29.4 (*c* 0.09, $CHCl_3$), 99% ee, $[\alpha]_D^{23}$ +29.7 (*c* 0.54, $CHCl_3$), 100% ee.

Enantiomerically enriched 2,2,2-trifluoro-1-(4-bromo-4'-biphenylyl)ethanol: ^1H NMR (270 MHz, $CDCl_3$): δ 2.60 (d, *J* = 4.62 Hz, 1H), 5.00 (d, q, *J* = 4.62, 6.60 Hz, 1H), 7.44-7.63 (m, 8H). ^{19}F NMR: δ -80.0 (d, *J* = 6.60 Hz). IR ($CHCl_3$): 1720, 1610, 1500, 1360, 1300, 1180, 1140 cm^{-1}. *R* and *S* form mp 115~117 °C (from *n*-hexane). HRMS (EI^+): calcd for $C_{14}H_{10}OF_3Br$ (M^+), 329.9867. found: 329.9821. *R* form, **2b** $[\alpha]_D^{23}$ -13.0 (*c* 6.0, $CHCl_3$), 78% ee; *S* form, **3b** $[\alpha]_D^{23}$ +17.1 (*c* 0.20, $CHCl_3$), 96% ee, $[\alpha]_D^{23}$ +17.6 (*c* 0.93, $CHCl_3$), 100% ee.

Enantiomerically enriched 2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol: ^1H NMR (270 MHz, $CDCl_3$): δ 2.63 (brs, 1H), 3.85 (s, 3H), 5.01 (q, *J* = 6.71 Hz, 1H), 6.97 (d, *J* = 8.54 Hz, 2H), 7.25-7.53 (m, 4H), 7.58 (d, *J* = 8.54 Hz, 2H). ^{19}F NMR : δ -80.0 (d, *J* = 6.71 Hz). IR ($CHCl_3$): 3580, 3340, 1610, 1500, 1460, 1350, 1300, 1130, 1000, 590, 550, 530 cm^{-1}. *R* and *S* form mp 131~133 °C (from *n*-hexane). HRMS (EI^+): calcd for $C_{15}H_{13}O_2F_3$ (M^+), 282.0868. found: 282.0840. *R* form, **2c** $[\alpha]_D^{23}$ -26.4 (*c* 1.12, $CHCl_3$), 98% ee, $[\alpha]_D^{23}$ -27.6 (*c* 0.42, $CHCl_3$), 100% ee; *S* form, **3c** $[\alpha]_D^{23}$ +26.0 (*c* 0.19, $CHCl_3$), 98% ee.

Enantiomerically enriched 2,2,2-trifluoro-1-(4-hydroxy-4'-biphenylyl)ethanol: ^1H NMR (270 MHz, $CDCl_3$): δ 2.60 (brs, 1H), 4.92 (brs, 1H), 5.06 (q, *J* = 6.93 Hz, 1H), 6.91 (d, *J* = 8.55 Hz, 2H), 7.48 (d, *J* = 8.55 Hz, 2H), 7.52 (d, *J* = 8.55 Hz, 2H), 7.58 (d, *J* = 8.55 Hz, 2H). ^{19}F NMR: δ -79.0 (d, *J* = 6.93 Hz). IR ($CHCl_3$): 3650, 3550, 3400, 1650, 1620, 1140, 650, 550, 530, 480 cm^{-1}. *R* and *S* form mp 157~159 °C (from *n*-hexane). HRMS (EI^+): calcd for $C_{14}H_{11}O_2F_3$ (M^+), 268.0711. found: 268.0697. *R* form, **2d** $[\alpha]_D^{23}$ -17.7 (*c* 0.78, $CHCl_3$), 60% ee, $[\alpha]_D^{23}$ -27.2 (*c* 0.39, $CHCl_3$), 100% ee; *S* form, **3d** $[\alpha]_D^{23}$ +26.7 (*c* 0.21, $CHCl_3$), 98% ee.

Enantiomerically enriched 2,2,2-trifluoro-1-(4-acetoxy-4'-biphenylyl)ethanol: ^1H NMR (270 MHz, $CDCl_3$): δ 2.26 (s, 3H), 2.64 (d, *J* = 4.27 Hz, 1H), 5.08 (d, q, *J* = 4.27, 6.10 Hz, 1H), 7.17 (d, *J* = 8.58 Hz, 2H), 7.56 -7.60 (m, 4H), 7.71 (d, *J* = 8.58 Hz, 2H). ^{19}F NMR: δ -79.0 (d, *J* = 6.10 Hz). IR ($CHCl_3$): 1780, 1480, 1140, 1280, 1180, 550, 530, 480 cm^{-1}. mp 167~169 °C (from *n*-hexane). HRMS (EI^+): calcd for $C_{16}H_{13}O_3F_3$ (M^+), 310.0817. found: 310.0829. *S* form, **3e** $[\alpha]_D^{23}$ +24.2 (*c* 0.07, $CHCl_3$), 98% ee, $[\alpha]_D^{23}$ +24.4 (*c* 0.39, $CHCl_3$), 100% ee.

Enantiomerically enriched 4-{4'-[(1-hydroxy-2,2,2-trifluoro)ethyl]phenyl}benzoic acid: Isolated by methyl esterification with CH_2N_2 at room temperature. ^1H NMR (270 MHz, $CDCl_3$): δ 2.76 (d, J = 4.29 Hz, 1H), 3.95 (s, 3H), 5.09 (d, q, J = 4.29, 6.90 Hz, 1H), 7.58 (d, J = 8.58 Hz, 2H), 7.65 (d, J = 8.58 Hz, 2H), 7.66 (d, J = 8.58 Hz, 2H), 8.11 (d, J = 8.58 Hz, 2H). ^{19}F NMR: δ -80.0 (d, J = 6.90 Hz). IR ($CHCl_3$): 3580, 3350, 1710, 1600, 1280, 1120 cm^{-1}. *R* and *S* form mp 133~135 °C (from *n*-hexane). HRMS (EI^+): calcd for $C_{16}H_{13}O_3F_3$ (M^+), 310.0817. found: 310.0772. *R* form, **2g** $[\alpha]_D^{23}$ -18.0 (*c* 0.10, $CHCl_3$), 69% ee; *S* form, **3g** $[\alpha]_D^{23}$ +25.5 (*c* 0.08, $CHCl_3$), 98% ee, $[\alpha]_D^{23}$ +26.1 (*c* 0.33, $CHCl_3$), 100% ee.

Enantiomerically enriched methyl 4-{4'-[(1-hydroxy-2,2,2-trifluoro)ethyl]phenyl} benzoate: ^1H NMR (270 MHz, $CDCl_3$): ^1H NMR (270 MHz, $CDCl_3$): δ 2.76 (d, J = 4.29 Hz, 1H), 3.95 (s, 3H), 5.09 (d, q, J = 4.29, 6.90 Hz, 1H), 7.58 (d, J = 8.58 Hz, 2H), 7.65 (d, J = 8.58 Hz, 2H), 7.66 (d, J = 8.58 Hz, 2H), 8.11 (d, J = 8.58 Hz, 2H). ^{19}F NMR: δ -80.0 (d, J = 6.90 Hz). IR ($CHCl_3$): 3580, 3350, 1710, 1600, 1280, 1120 cm^{-1}. *R* and *S* form mp 133~135 °C (from *n*-hexane). HRMS (EI^+): calcd for $C_{16}H_{13}O_3F_3$ (M^+), 310.0817. found: 310.0772. *R* form, **2g** $[\alpha]_D^{23}$ -23.2 (*c* 0.65, $CHCl_3$), 89% ee; *S* form, **3g** $[\alpha]_D^{23}$ +24.7 (*c* 0.12, $CHCl_3$), 96% ee, $[\alpha]_D^{23}$ +26.1 (*c* 0.33, $CHCl_3$), 100% ee.

Enantiomerically enriched 2,2,2-trifluoro-1-(4-amino-4'-biphenylyl)ethanol: ^1H NMR (270 MHz, $CDCl_3$): δ 2.63 (brs, 1H), 3.75 (brs, 2H), 5.00 (q, J = 6.71 Hz, 1H), 6.75 (d, J = 8.58 Hz, 2H), 7.41 (d, J = 8.58 Hz, 2H), 7.45 (d, J = 8.58 Hz, 2H), 7.56 (d, J = 8.58 Hz, 2H). ^{19}F NMR : δ -79.5 (d, J = 6.71 Hz). IR ($CHCl_3$): 3650, 3550, 3400, 1650, 1620, 1140, 650 cm^{-1}. *R* and *S* form mp 141~149 °C (from *n*-hexane). HRMS (EI^+): calcd for $C_{14}H_{12}ONF_3$ (M^+), 267.0871. found: 267.0830. *R* form, **2h** $[\alpha]_D^{23}$ -17.7 (*c* 0.18, $CHCl_3$), 58% ee; *S* form, **3h** $[\alpha]_D^{23}$ +29.3 (*c* 0.35, $CHCl_3$), 96% ee, $[\alpha]_D^{23}$ +30.6 (*c* 0.91, $CHCl_3$), 100% ee.

The authentic sample of (*R*)-2,2,2-trifluoro-1-biphenylylethanol 2a: To a Grignard reagent **5** (2.4 ml, 2.14 *N*, 5.22 mmol) prepared from bromobenzene was added dropwise a THF solution (5 ml) of $Pd(PPh_3)_4$ prepared from $Pd(OAc)_2$ (39.1 mg, 0.174 mmol), PPh_3 (456.4 mg, 1.74 mmol) and *n*-BuLi (0.1 ml, 0.176 mmol, 1.71 *N* in a hexane solution) at 0 °C for 10 min, and the mixture was stirred for 30 min. To the resulting mixture was added dropwise a solution of (*R*)-2,2,2-trifluoro-1-(4'-bromophenyl)ethanol (444.7 mg, 1.74 mmol, 32% ee) in THF (5 ml) at room temperature for 10 min, and the mixture was refluxed for 9 h, cooled, and quenched by aq. NaCl. The entire mixture was extracted with CH_2Cl_2 (10 ml x 3). The combined extracts were dried with Na_2SO_4, and the solvent was removed. The title compound was obtained on slica gel thin layer chromatography (200 mg, 46%). *R* form, $[\alpha]_D^{23}$ -4.2 (*c* 1.7, $CHCl_3$), 14% ee. mp 124~125 °C ^1H NMR, ^{19}F NMR and IR spectra of **2a** were identical with those of 2,2,2-trifluoro-1-biphenylylethanol previously described.

The authentic sample of (*R*)-2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol 2c: Grignard reagent **7** prepared from 4-bromoanisol (1 g, 5.3 mmol) and magnesium (141.7 mg, 5.83 mmol) in THF (40 ml), $Pd(PPh_3)_4$ prepared from $Pd(OAc)_2$ (39.5 mg, 0.176 mmol), PPh_3 (461.6 mg, 1.76 mmol) and *n*-BuLi (0.1 ml, 0.176 mmol, 1.71 *N* in a hexane solution) and (*R*)-2,2,2-trifluoro-1-(4'-bromophenyl)ethanol[16] (450 mg, 1.76 mmol, 32% ee) were used as in the case of the authentic sample **2a**. The title compound was purified on slica gel thin layer chromatography (225 mg, 45%). *R* form, $[\alpha]_D^{23}$ -3.4 (*c* 0.29, $CHCl_3$), 13% ee. mp 131~133 °C. ^1H NMR, ^{19}F NMR and IR spectra of **2c** were identical with those of 2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol previously described.

The authentic sample of (*S*)-2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol 3c from 3d: To a THF solution (3 ml) of (*S*)-2,2,2-trifluoro-1-(4-hydroxy-4'-biphenylyl)ethanol **3d** (48.3 mg, 0.18 mmol, 86% ee) obtained by the reduction of *Geotrichum candidum* acetone powder was added KHMDS (0.56 ml, 0.22 mmol of a 0.5*M* toluene solution) at 0 °C. After 30 min stirring, a solution of MeI (25.5 mg, 0.18 mmol) in THF (1 ml) was added to the resulting mixture at 0 °C for 15 min. After stirring for 3 h, the reaction was quenched by aq. NaCl. The entire mixture was extracted with ethyl acetate (10 ml x 3). The combined extracts were dried with Na_2SO_4, and the solvent was removed. The title compound was obtained

on slica gel thin layer chromatography (37.3 mg, 74%). *S* form, $[\alpha]_D^{23}$ +23.5 (*c* 0.68, $CHCl_3$), 85% ee. mp 131~133 °C. ^1H NMR, ^{19}F NMR and IR spectra were identical with those of 2,2,2-trifluoro-1-(4-methoxy-4'-biphenylyl)ethanol previously described.

The authentic sample of (*S*)-2,2,2-trifluoro-1-(4-hydroxy-4'-biphenylyl)ethanol 3d from 3e: To a methanol solution (0.5 ml) containing (*S*)-2,2,2-trifluoro-1-(4-acetoxy-4'-biphenylyl)ethanol **3e** (10.5 mg, 0.034 mmol, 98% ee) was added 1 ml of saturated sodium aq. bicarbonate solution. After the mixture was allowed to stand for 1 h at room temperature, it was acidified with 10% hydrochloric acid, extracted with ethyl acetate, washed with water, and dried with Na_2SO_4. Then the solvent was removed. The title compound was obtained on slica gel thin layer chromatography (5.3 mg, 69%). *S* form, $[\alpha]_D^{23}$ + 26.7 (*c* 0.1, $CHCl_3$), 98% ee. mp 157~159 °C. ^1H NMR, ^{19}F NMR and IR spectra were identical with those of 2,2,2-trifluoro-1-(4-hydroxy-4'-biphenylyl)ethanol previously described.

The authentic sample of (*S*)-2,2,2-trifluoro-1-biphenylethanol 3a from 3b: To a THF solution (2 ml) of (*S*)-2,2,2-trifluoro-1-(4-bromo-4'-biphenylyl)ethanol **3b** (10 mg, 0.03 mmol, 98% ee) obtained by the reduction with *Geotrichum candidum* acetone powder was added dropwise a solution of *n*-BuLi (0.04 ml, 0.066 mmol, 1.71 *N* in a hexane solution) at -78 °C. After 3 h stirring, the reaction was quenched by aq. NaCl. The entire mixture was extracted with ethyl acetate (10 ml x 3). The combined extracts were dried with Na_2SO_4, and the solvent was removed. The title compound was obtained on slica gel thin layer chromatography (33 mg, 45%). *S* form, $[\alpha]_D^{23}$ +29.1 (*c* 0.04, $CHCl_3$), 98% ee. mp 124~125 °C. ^1H NMR, ^{19}F NMR and IR spectra were identical with those of 2,2,2-trifluoro-1-biphenylethanol previously described.

The authentic sample of (*S*)-2,2,2-trifluoro-1-(4-bromo-4'-biphenylyl)ethanol 3b from 3g: To a MeOH solution (2 ml) of (*S*)-methyl 4-{[4'-(1-hydroxy-2,2,2-trifluoro)ethyl]phenyl}benzoate **3g** (10 mg, 0.03 mmol, 96% ee) prepared by the reduction of *Geotrichum candidum* acetone powder was added a solution KOH (1 g, 17.8 mmol) in H_2O (3 ml) at 0 °C. After 2 h stirring, the reaction was quenched by aq. 2 *N* HCl. The entire mixture was extracted with ethyl acetate (5 ml x 3). The combined extracts were dried with Na_2SO_4, and solvent was removed. To 1% aq. sodium hydroxide solution (0.2 ml) and silver nitrate (6.4 mg, 0.038 mmol) was added the benzoic acid (10.1 mg, 0.034 mmol) from **3g**. The precipitate was filtered, washed well with water, dried to constant weigh at 100~105 °C, and dried in a desiccator over phosphorus pentoxide. The resulting silver salt (13.7 mg, 0.034 mmol) was suspended in carbon tetrachloride (2 ml), and bromine (3.4 ml) was added dropwise at room temperature. The solution was stirred for 5 h at refluxing temperature, and the hot solution was filtered. The filtrate was washed with aq. sodium bisulfite followed by aq. sodium bicarbonate solution. The title compound was obtained on slica gel thin layer chromatography (2 mg, 20%). *S* form, $[\alpha]_D^{23}$ +15.0 (*c* 0.04, $CHCl_3$), 85% ee. mp 115~117 °C. ^1H NMR, ^{19}F NMR and IR spectra were identical with those of 2,2,2-trifluoro-1-(4-bromo-4'-biphenylyl)ethanol previously described.

The authentic sample of (*S*)-2,2,2-trifluoro-1-(4-bromo-4'-biphenylyl)ethanol 3b from 3h: To a solution of conc. H_2SO_4 (0.05 ml), MeOH (0.1 ml), and H_2O (0.2 ml) was added a solution of (*S*)-2,2,2-trifluoro-1-(4-amino-4'-biphenylyl)ethanol **3h** (10 mg, 0.04 mmol, 96% ee) in MeOH (0.1 ml) at 0 °C for 10 min. To the mixture was added dropwise a solution of $NaNO_2$ (3.45 mg, 0.05 mmol) in H_2O (0.2 ml) at 0 °C. After 30 min stirring, to the resulting mixture was added dropwise a solution prepared from CuBr (2.9 mg, 0.02 mmol), 47% HBr (0.2 ml) and H_2O (0.1 ml). The resulting mixture was stirred for 3 h at refluxing temperature. The mixture was filtered through a celite pad. The entire mixture was extracted with ethyl acetate (5 ml x 3). The combined extracts were dried with Na_2SO_4, and the solvent was removed. The title compound was obtained on slica gel thin layer chromatography (2.9 mg, 22%). *S* form, $[\alpha]_D^{23}$ +16.8 (*c* 0.04, $CHCl_3$), 96% ee. mp 115~117 °C. ^1H NMR, ^{19}F NMR and IR spectra were identical with those of 2,2,2-trifluoro-1-(4-bromo-4'-biphenylyl)ethanol previously described.

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