Baker's Yeast Reduction of α-(Acylamino)acetophenones and Lipase Catalyzed Resolution of 2-Acylamino-1-arylethanols

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Enzymatic reduction of α-acylaminoacetophenones with fermenting baker's yeast afforded optically active (*R*)-2-acylamino-1-arylethanols. Furthermore, lipase-catalyzed resolution of the 2-acylamino-1-arylethanols using vinyl acetate as an acyl donor resulted in the formation of (*S*)-1-acetoxy-2-acylamino-1-arylethanols and (*R*)-2-acylamino-1-arylethanols.

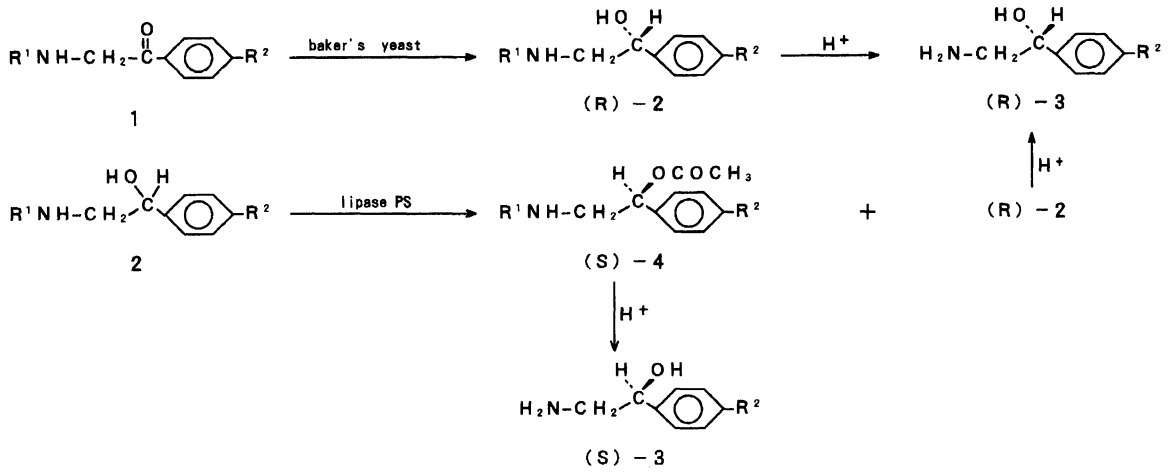
Enzymatic catalysis has recently been used for the optical resolution of several highly functionalized chiral molecules such as amino acids, diesters, diols, lactones, and hydroxy acids.[1)] Surprisingly, very little attention has been paid to the enzymatic resolution of chiral 2-amino-1-arylethanols in spite of their importance as chiral auxiliaries, chiral building blocks, and biologically active compounds. There are only a few reports on the enantioselective reduction of α-aminoketones using baker's yeast[2)] and on the resolution of chiral amino alcohols with hydrolytic enzymes.[3)] Recently, Kanerva et al.[4)] reported that the lipase PS- and CCL-catalyzed resolution of unsubstituted and *N*-alkyl-substituted 2-amino-1-phenylethanols with 2,2,2-trifluoroethyl butyrate or with butyric anhydride resulted in the formation of (*S*)-butyrates and (*R*)-alcohols. However, the baker's yeast-catalyzed reduction of the corresponding ketones cannot compete with the lipase-catalyzed resolution due to the low chemical yield and low optical purity. In this paper, we wish report our work related to the enzymatic reduction of α-(acylamino)-acetophenones (**1**) using baker's yeast and the kinetic resolution of 2-acylamino-1-arylethanols (**2**) using lipase PS (Scheme 1).

Results and Discussion

Baker's Yeast Reduction of α-(Acylamino) acetophenones (1). Baker's yeast-mediated reduction of ketones often gives highly optically pure secondary alcohols.[1b)] In an initial attempt, asymmetric reduction of α-(acetamido) acetophenone (**1a**) was performed by incubation with fermenting baker's yeast for 21 d at 32°C, and the enzymatic reduction of **1a** to (−)-(*R*)-2-acetamido-1-phenylethanol [(***R***)-**2a**] was easily achieved by baker's yeast reduction even though the enantiomeric excess value (ee) of the product was poor (ee=26%). We then turned our attention to improving the optical yield in the reduction of **1** by introducing a variety of substituents to the *p*-position of the phenyl group, and by changing the *N*-protecting group. The results of the yeast reduction of **1a-j** are summarized in Table 1. The absolute configurations of the products **2a-j** were assigned by comparison of the optical rotation with the literature data, after transformation by hydrolysis with hydrochloric acid to the authentic (*R*)-(−)-2-amino-1-arylethanols (**3a-e**). The optical purities (ee) of **2a-j** were determined by chiral HPLC analysis with a Daicel chiralcel OG column. As the substituent of the phenyl group, the choice of the halo substitutents markedly increased both the chemical and optical yields, and the increasing order of the ee values was in parallel with that of the bulkiness of the halogens (Entries 2 and 3). Furthermore, the methoxy substituent greatly improved the ee to 99%, although the chemical yield was not so high (Entry 5). On the other hand, the choice of the benzoyl and *p*-tolylsulfonyl groups as the *N*-protecting group also increased the ee value (Entires 7 and 8), however, the yeast reduction of trifluoroacetyl derivative **1f** was very slow and the optical yield was low (Entry 6).

We have shown that baker's yeast reduction of **1** leads to products with an *R*-configuration. This result could be explained assuming that, following the Prelog's rule,[5)] in compounds **1a-j** the acylamino moiety is "effectively smaller" than the aromatic moiety.

Lipase PS Resolution of 2-Acylamino-1-arylethanols (2). A kinetic study of the acylation of racemic 2-acetamido-1-phenylethanol **2a** was undertaken in several organic solvents, using lipase from *Pseudomonas cepacia* (lipase PS, Amano) and vinyl acetate as the acyl donor. In the presence of a molecular sieve, the reactions were carried out at 25 °C, and the conversion was monitored by TLC. Remarkably, in diisopropyl ether or a mixture of hexane and THF (3:2), the reaction proceeded at a reasonable rate of up to 50% conversion. In other solvents, such as chloroform and acetonitrile, the reaction became much slower. To isolate the products, in a further experiment the reaction in diisopropyl ether was stopped after 36 h (45% conversion) by filtration to remove the enzyme, and the resulting acetate [(***S***)-**4a**] and the unreacted alcohol [(***R***)-**2a**] were separated by column chromatography in 43 and 47% yields, respectively. The results and the analytical data of the products are summarized in Tables 2 and 3, respectively. The optical purities of acetate (***S***)-**4a** and of unreacted alcohol (***R***)-**2a** were high (ee>99% and 92%, respectively). Therefore, the enantiomeric ratio (*E*)[6)] of this kinetic resolution was excellent (*E*>500) (Entry 2). The *S*-configuration for acetate **4a** and the *R*-configuration for unreacted alcohol **2a** were deter-



1a, 2a, (R)−2a, (S)−4a : R^1=−$COCH_3$, R^2=−H
1b, 2b, (R)−2b, (S)−4b : R^1=−$COCH_3$, R^2=−Cl
1c, 2c, (R)−2c, (S)−4c : R^1=−$COCH_3$, R^2=−Br
1d, 2d, (R)−2d, (S)−4d : R^1=−$COCH_3$, R^2=−CH_3
1e, 2e, (R)−2e, (S)−4e : R^1=−$COCH_3$, R^2=−OCH_3
1f, 2f, (R)−2f, (S)−4f : R^1=−$COCF_3$, R^2=−H
1g, 2g, (R)−2g, (S)−4g : R^1=−COPh, R^2=−H
1h, 2h, (R)−2h, (S)−4h : R^1=−$SO_2C_6H_4CH_3$-p, R^2=−H
1i, 2i, (R)−2i, (S)−4i : R^1=−CO−C_4H_3S(2−), R^2=−H
1j, 2j, (R)−2j, (S)−4j : R^1=−COOEt, R^2=−H

(R)−3a, (S)−3a : R^2=−H
(R)−3b, (S)−3b : R^2=−Cl
(R)−3c, (S)−3c : R^2=−Br
(R)−3d, (S)−3d : R^2=−CH_3
(R)−3e, (S)−3e : R^2=−OCH_3

Scheme 1.

Table 1. Enzymatic Reduction of α-(Acylamino) acetophenone Derivatives **1** Using Baker's Yeast

Entry	Substrate	Time d	Product[a] Config.	Yield %	Mp °C	$[\alpha]_D^{20}$/° (c, $CHCl_3$)	ee[b] %	Hydrolysis product of **2** Config.	$[\alpha]_D^{20}$/°	(solvent)	ee[b] %
1	**1a**	21	(*R*)-**2a**	19	134—137	−22.5(0.75)	26.2	(*R*)-**3a**	−12.3	(EtOH)[c]	26.0
2	**1b**	21	(*R*)-**2b**	70	135—138	−53.8(0.10)	90.5	(*R*)-**3b**	−58.2	($CHCl_3$)[d]	89.5
3	**1c**	21	(*R*)-**2c**	77	130—131	−80.9(0.49)	94.5	(*R*)-**3c**	−38.6	(EtOH)[e]	94.0
4	**1d**	21	(*R*)-**2d**	25	136—138	−59.4(0.45)	42.7	(*R*)-**3d**	−21.6	(Et_2O)[d]	41.4
5	**1e**	21	(*R*)-**2e**	71	88—89	−72.4(0.15)	99.4	(*R*)-**3e**	−39.2	(EtOH)[g]	99.0
6	**1f**	21	(*R*)-**2f**	23	80—82	−16.9(0.13)	5.6	(*R*)-**3f**	−2.6	(EtOH)[c]	5.1
7	**1g**	21	(*R*)-**2g**	52	144—147	−65.4(0.93)	91.0	(*R*)-**3a**	−41.2	(EtOH)[c]	90.2
8	**1h**	21	(*R*)-**2h**	76	97—99	−77.2(0.24)	94.3	(*R*)-**3a**	−42.3	(EtOH)[c]	94.3
9	**1i**	21	(*R*)-**2i**	43	101—104	−41.2(0.56)	68.3	(*R*)-**3a**	−29.8	(EtOH)[c]	67.8
10	**1j**	21	(*R*)-**2j**	40	92—94	−31.8(0.48)	63.5	(*R*)-**3a**	−28.1	(EtOH)[c]	63.0

a) The absolute configurations of the products were determined on the basis of those of 2-amino-1-arylethanols (**3**) obtained by hydrolysis with 10% hydrochloric acid in methanol. The spectroscopic data were identical with those of **2a-j**. b) The enantiomeric purity was determined by chiral HPLC analysis with a Daicel chiralcel OG column. c) Mp 53—57°C {Lit,[16] mp 54—58°C and $[\alpha]_D^{20}$ −42.2° (c 1, EtOH), 95% ee}. d) Mp 96—98°C {Lit,[17] mp 97.2—98.5°C and $[\alpha]_D$ −64.3° (c 1, $CHCl_3$)}. e) Mp 124—126°C. The absolute configuration was determined by transformation (catalytic reduction using palladium–carbon catalyst in ethanol) to (*R*)-**3a**. f) Mp 75—77°C {Lit,[18] mp 76—78°C and $[\alpha]_D^{20}$ −49° (c 0.6, Et_2O)}. g) Mp 100—102°C {Lit,[16] mp 102—103°C and $[\alpha]_D^{20}$ −38.6° (c 1, EtOH), 96% ee}.

mined according to the optical rotations given in the literature after conversion by hydrolysis with 10% hydrochloric acid to the corresponding 2-amino-1-phenylethanols [(*S*)-**3a** and (*R*)-**3a**, respectively]. In analogy with the baker's yeast reduction of **1**, modifying the phenyl group of **2** with halo substituents also increased the optical yield even though the reaction rates were much slower (Entries 5 and 6). The methyl and methoxy substituents also showed high ee values, although the chemical yields were rather low (Entries 8 and 9). Moreover, the choice of the 2-thenoylcarbonyl and ethoxycarbonyl substituents as *N*-protecting group also increased the ee value to 99% (Entries 12 and 13). It is also obvious from Table 2 that the enantioselectivity using lipase PS decreased when the protecting group in amino alcohol **2** was changed from the acetyl of **2a** to the trifluoroacetyl of **2f** or the *p*-tolylsulfonyl of **2h** (Entries 10 and 12). In summary, lipase PS-catalyzed transesterification of **2** has *S*-specificity and is a novel enzymatic approach to obtain simultaneously both enantiomers of the racemate with high optical purity. Recently, Kazlauskas et al.[7] proposed a rule similar to Prelog's rule for pre-

Table 2. Enzymatic Resolution of 2-Acylamino-1-arylethanols **2** Using Lipase-P

Entry	Substrate	Solvent[a]	Time	Conversion[b]	Produced acetate[c]			Unreacted alcohol[c]			E[e]
					Config.	Yield[d]	ee	Config.	Yield[d]	ee	
			h	%		%	%		%	%	
1	**2a**	A	27	43	(*S*)-**4a**	40	98	(*R*)-**2a**	48	82	220
2	**2a**	B	36	45	(*S*)-**4a**	43	99	(*R*)-**2a**	47	92	500
3	**2a**	C	72	28	(*S*)-**4a**	27	76	(*R*)-**2a**	68	48	10
4	**2a**	D	72	30	(*S*)-**4a**	27	68	(*R*)-**2a**	66	42	7
5	**2b**	A	168	44	(*S*)-**4b**	41	99	(*R*)-**2b**	40	99	470
6	**2c**	A	192	48	(*S*)-**4c**	46	99	(*R*)-**2c**	45	99	645
7	**2d**	A	96	27	(*S*)-**4d**	26	95	(*R*)-**2d**	73	25	55
8	**2e**	A	84	40	(*S*)-**4e**	38	94	(*R*)-**2e**	58	35	60
9	**2f**	A	240	30	(*S*)-**4f**	30	24	(*R*)-**2f**	68	28	2
10	**2g**	A	120	28	(*S*)-**4g**	22	88	(*R*)-**2g**	66	48	20
11	**2h**	A	240	20	(*S*)-**4h**	17	49	(*R*)-**2h**	68	18	3
12	**2i**	A	48	40	(*S*)-**4i**	39	99	(*R*)-**2i**	59	43	400
13	**2j**	A	240	45	(*S*)-**4j**	42	96	(*R*)-**2j**	54	85	120

a) A: a mixture (100 ml) of hexane and THF (3:2). B: diisopropyl ether (80 ml). C: chloroform (80 ml). D: acetonitrile (80 ml). b) Determined by GLC by comparison with an internal standard. c) The absolute configuration of (*S*)-**4** and (*R*)-**2** were assigned by transformation (hydrolysis by 10% hydrochloric acid in methanol) to (*S*)- and (*R*)-2-amino-1-arylethanols (**3**), respectively. d) Isolated yield. e) Enantiomeric ratio:[6] $E=\ln[1-c(1+ee_p)]/[1-c(1-ee_p)]$, $c=ee_p/ee_s+ee_p$.

Table 3. Properties of the Optically Active 2-Acylamino-1-arylethanols (*R*)-**2** and (*S*)-**4**

Compound	Mp (°C); $[\alpha]_D^{20}$ (c, $CHCl_3$); IR (cm^{-1}); ^1H NMR ($CDCl_3$)/δ; MS m/z (M^+); Anal. Found (calcd)/%.
(*S*)-**4a**[a]	Colorless oil; [α] +59.8 (0.27); IR (neat) 3300, 1740, 1660, 760, and 700; ^1H NMR 1.92 (s, 3H), 2.09 (s, 3H), 3.62 (br-s, 2H), 5.86 (d-d, 1H), 6.42 (br-s, 1H), and 7.34 (s, 5H); m/z 221; C, 65.04; H, 6.72; N, 6.25 (C, 65.14; H, 6.83; N, 6.33).
(*R*)-**2a**[b]	Colorless crystals; mp 134—137°C; [α] −79.0 (0.33); spectroscopic data were identical to **2a**.
(*S*)-**4b**[c]	Colorless crystals, mp 81—82°C; [α] +61.9 (0.50); IR (neat) 3280, 1730, 1660, and 820; ^1H NMR 1.92 (s, 3H), 2.08 (s, 3H), 3.58 (br-s, 2H), 5.83 (d-d, 1H), 6.08 (br-s, 1H), 7.36 (s, 4H); m/z 255, 257; C, 56.30; H, 5.41; N, 5.41 (C, 56.36; H, 5.52; N, 5.48).
(*R*)-**2b**[d]	Colorless crystals; mp 135—138°C; [α] −59.5 (c 0.68); spectroscopic data were identical to **2b**.
(*S*)-**4c**[e]	Colorless crystals, mp 75—76°C; [α] +50.1 (0.78); IR (neat) 3270, 1720, 1650, and 820; ^1H NMR 1.94 (s, 3H), 2.10 (s, 3H), 3.64 (br-s, 2H), 5.78 (d-d, 1H), 6.05 (br-s, 1H), 7.18 (d, 2H), and 7.48 (d, 2H); m/z 300; C, 47.92; H, 4.57; N, 4.55 (C, 48.02; H, 4.70; N, 4.67).
(*R*)-**2c**[f]	Colorless crystals; mp 131—133°C; [α] −85.6 (0.14); spectroscopic data were identical to **2c**.
(*S*)-**4d**[g]	Colorless oil; [α] +62.3 (0.47); IR (neat) 3300, 1740, 1660, and 820; ^1H NMR 1.90 (s, 3H), 1.95 (s, 3H), 2.08 (s, 3H), 3.59 (m, 2H), 5.85 (m, 1H), 6.38 (br-s, 1H), 7.11 (d, 2H), and 7.26 (d, 2H); m/z 235; C, 66.19; H, 7.21; N, 5.86 (C, 66.36; H, 7.28; N, 5.95).
(*R*)-**2d**[h]	Colorless crystals, mp 136—138°C; [α] −75.2 (0.27); spectroscopic data were identical to **2d**.
(*S*)-**4e**[i]	Colorless oil; [α] +72.6 (0.65); IR (neat) 3280, 1740, 1660, and 820; ^1H NMR 1.92 (s, 3H), 2.10 (s, 3H), 3.61 (m, 2H), 3.75 (s, 3H), 5.48 (m, 1H), 6.58 (br-s, 1H), 7.06 (d, 2H), and 7.46 (d, 2H); m/z 251; C, 62.21; H, 6.89; N, 5.65 (C, 62.14; H, 6.82; N, 5.57).

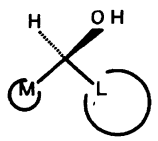


Fig. 1.

dicting the fast-reacting enantiomer in the resolution of secondary alcohols mediated by lipase PS (Fig. 1), and suggested a strategy for improving the efficiency of resolutions catalyzed by the enzyme: Secondary alcohols having substituents which differ significantly in size should be more efficiently resolved than secondary alcohols having substituents which are similar in size. Furthermore, as a working hypothesis to identify substrates that could be resolved with high enantioselectivity via biocatalytic acylations mediated by a lipase from *Pseudomonas sp.*, Burgess and Jennings[8] assumed that the alcohols that are resolved most efficiently have one "small" and one relatively "large" group attached to the hydroxymethine functionality. Our results from the enzymatic resolution of **2** with lipase PS do not obey these rules, and, in compound **2**, the "small" substituent is acylaminometyl and the "large" substituent is phenyl.

Experimental

All melting points were taken with a Gallenkamp melting point apparatus and are uncorrected. IR spectra were

Table 3. (Continued)

Compound	Mp (°C); $[\alpha]_D^{20}$ (c, $CHCl_3$); IR (cm^{-1}); ^1H NMR ($CDCl_3$)/δ; MS m/z (M^+); Anal. Found (calcd)/%.
(*R*)-**2e**[j]	Colorless crystls; mp 87—89°C; $[\alpha]$ −43.7 (0.41); spectroscopic data were identical to **2e**.
(*S*)-**4f**[k]	Colorless oil, $[\alpha]$ +22.4 (0.32); IR (neat) 3300, 1740, 1660, 750, and 690; ^1H NMR 2.13 (s, 3H), 3.68 (m, 2H), 5.69 (m, 1H), 6.72 (br-s, 1H), and 7.18 (m, 5H); m/z 275; C, 52.30; H, 4.51; N, 4.97 (C, 52.36; H, 4.38; N, 5.09).
(*R*)-**2f**[l]	Colorless crystals, mp 80—82°C; $[\alpha]$ −55.2 (0.18); spectroscopic data were identical to **2f**.
(*S*)-**4g**[m]	Colorless crystals, mp 110—112°C; $[\alpha]$ +40.7 (0.43); IR (KBr) 3320, 1730, 1640, 750, and 700; ^1H NMR 2.11 (s, 3H), 3.65 (m, 2H), 5.81 (m, 1H), 6.55 (br-s, 1H), 7.36 (m, 8H), and 7.68 (d-d, 2H); m/z 283; C, 71.97; H, 5.93; N, 4.86 (C, 72.07; H, 6.05; N, 4.94).
(*R*)-**2g**[n]	Colorless crystals, mp 145—148°C; $[\alpha]$ −34.5 (0.46); spectroscopic data were identical to **2g**.
(*S*)-**4h**[o]	Colorless crystals, mp 56—58°C; $[\alpha]$ +19.5 (0.34); IR (KBr) 3280, 1740, 1330, 1160, 810, 760, and 700; ^1H NMR 2.13 (s, 2H), 2.48 (s, 3H), 3.62 (m, 2H), 5.84 (m, 1H), 6.84 (br-s, 1H), 7.33 (s, 5H), and 7.65 (s, 4H); m/z 319; C, 60.06; H, 5.31; N, 4.32 (C, 60.17; H, 5.37; N, 4.39).
(*R*)-**2h**[p]	Colorless crystals, mp 97—100°C; $[\alpha]$ −14.8 (0.97); spectroscopic data were identical to **2h**.
(*S*)-**4i**[q]	Colorless oil; $[\alpha]$ +41.6 (1.05); IR (neat) 3320, 1730, 1640, 760, 720, and 700; 2.10 (s, 3H), 3.58 (m, 2H), 5.66 (m, 1H), 6.58 (br-s, 1H), 7.01 (m, 1H), and 7.28—7.51 (m, 7H); m/z 289; C, 62.17; H, 5.15; N, 4.76 (C, 62.26; H, 5.23; N, 4.84).
(*R*)-**2i**[r]	Colorless crystals, mp 100—104°C; $[\alpha]$ −25.8 (0.86); spectroscopic data were identical to **2i**.
(*S*)-**4j**[s]	Colorless oil, $[\alpha]$ +54.2 (0.68); IR (neat) 3320, 1730, 1710, 750, and 700; ^1H NMR 1.16 (t, 3H), 2.10 (s, 3H), 3.63 (m, 2H), 4.02 (q, 2H), 5.58 (m, 1H). 6.50 (br-s, 1H), and 7.23 (s, 5H); m/z 251; C, 62.21; H, 6.93; N, 6.65 (C, 62.14; H, 6.82; N, 5.57).
(*R*)-**2j**[t]	Colorless crystals, mp 91—94°C; $[\alpha]$ −42.1 (0.72); spectroscopic data were identical to **2j**.

a) The product of Entry 2 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-2-amino-1-phenylethanol (*S*)-**3a**, mp 58—61°C, $[\alpha]_D^{20}$ +44.0° (c 0.76, EtOH) {lit,[19] mp 61—63°C, $[\alpha]_D^{23}$ +44.8° (c 0.2088, EtOH)}. b) The product of Entry 2 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-2-amino-1-phenylethanol (*R*)-**3a**, mp 53—57°C, $[\alpha]_D^{20}$ −38.5° (c 0.65, EtOH) {lit,[16] mp 54—58°C, $[\alpha]_D^{20}$ −42.2° (c 1, EtOH)}. c) The product of Entry 5 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-2-amino-1-(4-chlorophenyl)ethanol (*S*)-**3b**, mp 96—98°C, $[\alpha]_D^{20}$ +65.1° (c 0.48, $CHCl_3$) {lit,[17] mp 97—98.6°C, $[\alpha]_D$ +65° (c 1, $CHCl_3$)}. d) The product of Entry 5 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-2-amino-1-(4-chlorophenyl)ethanol (*R*)-**3b**, mp 96—98°C, $[\alpha]_D^{20}$ −64.5° (c 0.48, $CHCl_3$) {lit,[17] mp 97.2—98.5°C (c 1, $CHCl_3$)}. e) The product of Entry 6 in Table 2. Hydrolysis with 10% hydrochloric acid and subsequent debromination using catalytic reduction afforded (*S*)-**3a**, mp 58—61°C, $[\alpha]_D^{20}$ +44.9° (c 0.34, EtOH). f) The product of Entry 6 in Table 2. Hydrolysis and subsequent debromination affordesd (*R*)-**3a**, mp 53—57°C, $[\alpha]_D^{20}$ −42.6° (c 0.78, EtOH). g) The product of Entry 7 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-2-amino-1-(4-methylphenyl)ethanol (*S*)-**3d**, mp 75—78°C, $[\alpha]_D^{20}$ +47.1° (c 0.41, Et2O) {lit,[18] (−)-isomer mp 76—78°C, $[\alpha]_D^{20}$ −49° (c 0.6, Et_2O)}. h) The product of Entry 7 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-**3d**, mp 76—78°C, $[\alpha]_D^{20}$ −12.5° (c 0.32, Et_2O). i) The product of Entry 8 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-2-amino-1-(4-methoxyphenyl) ethanol (*S*)-**3e**, mp 99—102°C, $[\alpha]_D^{20}$ +36.4° (c 0.48, EtOH) {lit,[16] (−)-isomer: mp 102—103°C, $[\alpha]_D^{20}$ −38.6° (c 1, EtOH)}. j) The product of Entry 8 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-**3e**, mp 100—102°C, $[\alpha]_D^{20}$ −14.0° (c 0.28, EtOH). k) The product of Entry 9 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-**3a**, mp 58—60°C, $[\alpha]_D^{20}$ +10.9° (c 0.21, EtOH). l) The product of Entry 9 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-**3a**, mp 54—57°C, $[\alpha]_D^{20}$ −12.0° (c 0.35, EtOH). m) The product of Entry 10 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-**3a**, mp 57—60°C, $[\alpha]_D^{20}$ +39.6° (c 0.62, EtOH). n) The product of Entry 10 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-**3a**, mp 54—57°C, $[\alpha]_D^{20}$ −20.4° (c 0.54, EtOH). o) The product of Entry 11 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-**3a**, mp 57—60°C, $[\alpha]_D^{20}$ +22.1° (c 0.45, EtOH). p) The product of Entry 11 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-**3a**, mp 54—57°C, $[\alpha]_D^{20}$ −7.7° (c 0.2, EtOH). q) The product of Entry 12 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-**3a**, mp 58—60°C, $[\alpha]_D^{20}$ +44.8° (c 0.36, EtOH). r) The product of Entry 12 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-**3a**, mp 53—58°C, $[\alpha]_D^{20}$ −18.3° (c 0.41, EtOH). s) The product of Entry 13 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*S*)-**3a**, mp 58—60°C, $[\alpha]_D^{20}$ +43.1° (c 0.56, EtOH). t) The product of Entry 13 in Table 2. Hydrolysis with 10% hydrochloric acid afforded (*R*)-**3a**, mp 53—58°C, $[\alpha]_D^{20}$ −36.2° (c 0.44, EtOH).

recorded a Hitachi 260-10 spectrometer, and ^1H NMR spectra were obtained with a Hitachi R-90H spectrometer, using TMS as an internal standard. Mass spectra were obtained from a Hitachi RMU-6M mass spectrometer. Optical rotations were measured on a JASCO DIP-140 digital polarimeter.

The enantiomeric purity of the products was determined by chiral HPLC analysis with a Daicel chiralcel OG column (4.6 mm×25 cm) with hexane-2-propanol (10 : 1) as the mobile phase at a flow rate of 0.5 ml min^{-1}.

Baker's yeast (*Saccharomyces cerevisiae*) and *Pseudomonas cepacia* lipase (Lipase PS) were purchased from Oriental Yeast Co. and Amano Pharmaceutical Co., respectively.

Preparation of α-(Acylamino)acetophenones (1). To a mixture of α-aminoacetophenone hydrochloride (15 mmol) and acyl chloride (20 mmol) was slowly added dry pyridine (40 ml) at 0°C with stirring. After the mixture was stirred for an additional 10 h at room temperature, the solvent was removed under reduced pressure. The residue was then poured into ice–water containing 10% hydrochloric acid, and the resultant precipitates were collected. Recrystallization from ethanol gave the product **1** in 64—85% yields.

Table 4. Properties of 2-Acylamino-1-arylethanols **2**

2	Yield %	Mp °C	IR (KBr) cm^{-1}	^1H NMR (DMSO-d_6)/δ	Anal. Found (Calcd) %
2a[a]	84	122—123	3270, 1640, 760, 700	1.82 (s, 3H), 3.11 (m, 2H), 4.40 (br-s, 1H), 4.61 (d-d, 1H), 7.28 (s, 5H), 7.84 (br-s, 1H)	a)
2b	85	120—121	3370, 3280, 1620, 830	1.81 (s, 3H), 3.13 (m, 2H), 4.62 (m, 1H), 5.50 (br-s, 1H), 7.33 (s, 4H), 7.83 (br-s, 1H)	C, 56.34; H, 5.76; N, 6.58 (C, 56.21; H, 5.66; N, 6.55)
2c	74	141—142	3290, 3220, 1640, 820	1.82 (s, 3H), 3.12 (m, 2H), 4.62 (br-s, 1H), 7.26 (d, 2H), 7.47 (d, 2H), 7.84 (br-s, 1H)	C, 46.58; H, 4.77; N, 5.51 (C, 46.53; H, 4.68; N, 5.42)
2d	81	152—153	3290, 3220, 1640, 810	1.92 (s, 3H), 2.31 (s, 3H), 3.22 (m, 2H), 3.65 (br-s, 1H), 4.73 (m, 1H), 6.27 (br-s, 1H), 7.10 (d, 2H), 7.24 (d, 2H)	C, 68.25; H, 7.76; N, 7.18 (C, 68.36; H, 7.82; N, 7.25)
2e	88	127—128	3350, 3250, 1630 820	2.13 (s, 3H), 3.15 (m, 2H), 3.78 (s, 3H), 4.48 (br-s, 1H), 4.85 (m, 1H), 6.78 (br-s, 1H), 7.08 (d, 2H), 7.43 (d, 2H)	C, 63.47; H, 6.91; N, 6.59 (C, 63.62; H, 7.02; N, 6.69)
2f[b]	90	78—79	3350, 3250, 1640, 750, 690	3.18 (m, 2H), 3.87 (br-s, 1H), 4.78 (m, 1H), 6.88 (br-s, 1H), 7.32 (s, 5H)	b)
2g[c]	90	146—147	3400, 3300, 1620, 760, 700	3.40 (m, 2H), 3.81 (m, 1H), 4.93 (br-s, 1H), 6.69 (br-s, 1H), 7.23—7.56 (m, 8H), 7.72 (d-d, 2H)	c)
2h[d]	87	108—109	3400, 3150, 1320, 1150, 810, 760, 700	2.45 (s, 3H), 3.22 (m, 2H), 3.63 (br-s, 1H), 4.85 (d-d, 1H), 7.15 (br-s, 1H), 7.36 (s, 5H), 7.76 (s, 2H), 7.85 (s, 2H)	d)
2i	93	105—106	3290, 3250, 1620, 750, 710, 690	3.40 (br-s, 1H), 3.82 (m, 2H), 4.86 (m, 1H), 6.72 (br-s, 1H), 6.98 (m, 1H), 7.20—7.47 (m, 7H)	C, 63.05; H, 5.22; N, 5.53 (C, 63.13; H, 5.30; N, 5.66)
2j[e]	88	89—90	3350, 3300, 1700, 760, 700	1.14 (t, 3H), 2.99—3.55 (m, 3H), 4.00 (q, 2H), 4.69 (d-d, 1H), 5.21 (br-s, 1H), 7.23 (s, 5H)	e)

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α-Acetamidoacetophenone (1a). Colorless crystals, mp 84—85°C (lit,[9] mp 86—87°C).

α-Acetamido-4-chloroacetophenone (1b). Colorless crystals, mp 174—176°C (lit,[10] mp 174—177°C).

α-Acetamido-4-bromoacetophenone (1c). Colorless crystals, mp 176—178°C (lit,[10] mp 175—177°C).

α-Acetamido-4-methylacetophenone (1d). Colorless crystals, mp 125—127°C (lit,[11] mp 127—128°C).

α-Acetamido-4-methoxyacetophenone (1e). Colorless crystals, mp 109—110°C (lit,[12] mp 109—110°C).

α-(Trifluoroacetamido)acetophenone (1f). Colorless crystals, mp 109—110°C (lit,[13] mp 108.5—110°C).

α-Benzamidoacetophenone (1g). Colorless crystals, mp 124—126°C (lit,[9] mp 123—125°C).

α-(*p*-Tolylsulfonylamino) acetophenone (1h). Colorless crystals, mp 115—116°C (lit,[14] mp 116°C).

α-(2-Thenoylmamino) acetophenone (1i). Colorless crystals, mp 114—116°C; IR (KBr) 3300 (–NH), 1690 (–C=O), 1610 (–NHCO–), 750, 680 (–Ph), and 720 cm^{-1} (thiophene ring); ^1H NMR ($CDCl_3$) δ=4.78 (2H, d, –C$\underline{H}_2$–), 6.82 (1H, br-s, –N$\underline{H}$), 6.94—6.98 (1H, m, thiophene-$\underline{H}_5$), and 7.24—7.51 (7H, m, Ph-$\underline{H}$+thiophene-$\underline{H}_3$+-$\underline{H}_4$); MS *m/z* 245 (M^+). Anal. Calcd for $C_{13}H_{11}NO_2S$: C, 63.65; H, 4.52; N, 5.71%. Found: C, 63.51; H, 4.44; N, 5.71%

α-(Ethoxycarbonylamino) acetophenone (1j). Colorless crystals, mp 57—58°C (lit,[15] mp 58°C).

Preparation of 2-Acylamino-1-arylethanols (2). To a solution of **1** (5.30 mmol) in ethanol (50 ml) at 0°C was slowly added sodium tetrahydroborate (0.2 g, 52.9 mmol) with stirring. After stirring for an additional 6 h at 0°C, the solvent was removed under reduced pressure. The residue was poured into ice water (500 ml) and the resultant mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was then recrystallized from ethanol in 75—90% yields. The spectroscopic and analytical data of the products are summarized in Table 4.

Baker's Yeast Reduction of 1. Baker's yeast (70 g) was dispersed in a solution of sucrose (70 g) in distilled water (700 ml), and the mixture was then stirred for 30 min

at 32°C. To the fermenting mixture was added dropwise a solution of **1a-j** (5.64 mmol) in ethanol (20 ml) for 30 min and incubated at the same temperature. Baker's yeast (5 g), sucrose (5 g), and distilled water (50 ml) were added to the reaction mixture every 2 d. After stirring for 21 d at 32 °C, the reaction was terminated by quenching with acetone (200 ml). After additional stirring for 30 min, the solution was filtered through a Celite pad and the solids were washed with methanol (2×300 ml). The combined filtrates were evaporated under reduced pressure to ca 300 ml, and the residue was extracted with $CHCl_3$ (2×200 ml). The $CHCl_3$ layers were dried with anhydrous $MgSO_4$ and evaporated in vacuo to give crude products. Column chromatography on silica gel (Wakolgel C-200, $CHCl_3$) afforded (*R*)-2-acylamino-1-arylethanol (***R***)-**2**. The absolute configurations of the products were determined according to the optical rotations given in the literature after conversion to (*R*)-2-amino-1-arylethanol (***R***)-**3** by hydrolysis with 10% hydrochloric acid in methanol. The results are given in Table 1.

Lipase PS-catalyzed Resolution of 2. To a mixture of (±)-**2** (4.0 mmol) in a solvent were successively added vinyl acetate (0.62 ml, 6.71 mmol), powdered 4 Å molecular sieve (1.0 g), and lipase PS (2.0 g), and the mixture was vigorously stirred at 25°C with monitoring by TLC. When the appropriate degree of conversion was reached, the reaction was terminated by filtration of the enzyme and the filtrate was evaporated to dryness under reduced pressure. Subsequent column chromatography of the residue (silica gel, $CHCl_3$) gave the (*S*)-acetate [(***S***)-**4**] and the (*R*)-alcohol [(***R***)-**2**]. The absolute configurations of the produced acetates [(***S***)-**4**] and the unreacted alcohols [(***R***)-**2**] were determined according to the optical rotations given in the literature after conversion by hydrolysis with 10% hydrochloric acid in methanol to the corresponding 2-amino-1-arylethanols [(***S***)-**3** and (***R***)-**3**, respectively]. The results and the spectroscopic data of the products are summarized in Tables 2 and 3, respectively.

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