Asymmetric Reduction of Ketones by the Acetone Powder of *Geotrichum candidum*

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Aromatic ketones, β-keto esters, and simple aliphatic ketones were reduced with excellent selectivity to the corresponding (*S*)-alcohols by using the acetone powder of *Geotrichum candidum*. This method is superior in reactivity and stereoselectivity to reduction by the whole-cell. The experimental conditions for the reduction system such as ratio of the biocatalyst to the substrate, kinds of coenzymes, alcohol for coenzyme regeneration, and buffer, pH, and reaction temperature were investigated, and stability and preservability of the biocatalyst were also examined. This method is very convenient for the synthesis of optically pure alcohols on a gram scale.

Introduction

The synthesis of enantiomerically pure compounds is becoming increasingly important for research and development in chemistry and biochemistry.[1] Among chiral compounds, enantiomerically pure alcohols are particularly useful as building blocks for the synthesis of natural products, pharmaceuticals, and agricultural chemicals since a variety of methods have been developed to convert the alcohol functionality to other useful functional groups such as chloride,[2] amine,[3] azide,[4] fluoride,[5] etc. One of the easiest methods for the preparation of optically active alcohols is the asymmetric reduction of ketones by either organometallic reagents with chiral ligands or biocatalysts such as alcohol dehydrogenases. Enzymatic reductions have attracted more and more attention due to the high stereoselectivities.[6] Currently, alcohol dehydrogenases from various sources such as baker's yeast,[7] horse liver (HLADH),[8] *Thermoanaerobium brockii* (TBADH),[9] *Thermoanaerobacter ethanolicus*,[10] *Lactobacillus kefir*,[11] *Pseudomonas sp.*,[12] *Gluconobacter oxidans*,[13] *Bacillus stearothermophilus*,[14] *Geotrichum candidum*,[15] et al. are used to reduce a full range of carbonyl compounds. Extensive research has been undertaken on the development of enzymatic systems for the asymmetric reduction of ketones, and many methods to control the stereochemistry of the reduction have been reported.[16]

However, there is still a need to improve the enantioselectivity of biocatalytic reduction. Although the selectivities of previously reported reduction systems were relatively high (around 90−95% ee) to moderate, enantiomerically pure compounds (>99% ee) could not be obtained except for a few cases. For example, the selectivity of the reduction of ketones by permeabilized cells of *Gluconobacter oxidans* is around 95% for most of its substrates (2-pentanone, 2-hexanone, 2-octanone, 3-nonanone, cyclohexyl methyl ketone), but a selectivity of 99% ee is obtained only for the reduction of acetophenone and methyl isopropyl ketone.[13]

Moreover, the substrate specificity of most of the systems is not wide enough to be beneficial for organic

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syntzhesis, some reasons being (1) the reactivity of HLADH is high for cyclic ketones but not for acyclic ketones,[8c] (2) the selectivity of TBADH is shown to be excellent for the reduction of only aliphatic ketones,[9] and (3) when the substrate specificity with reduction by the whole cell, such as baker's yeast which is easy to manipulate and commercially available, is very wide, the selectivity is low.[7b]

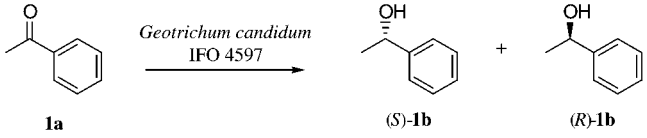
An easily available and handy biocatalyst with very high selectivity toward the reduction of any ketones, either aromatic or aliphatic, under mild reaction conditions would be of great value. Here, we report an enzymatic reduction system by which both aromatic and aliphatic ketones can be reduced with excellent stereoselectivity, resulting in the synthesis of secondary alcohols with a high yield and >99% ee. It should be emphasized that the biocatalyst for the system is easy to prepare and handle, the reaction proceeds under mild conditions, and the product isolation is simple. Another advantage of this system is that it is environmentally friendly.

A biocatalyst prepared from a dimorphic fungus, *Geotrichum candidum* IFO 4597, was employed for the reduction of ketones owing to its high reactivity with unnatural substrates and the simplicity of its growth. We used the acetone powder[17] of *G. candidum* (APG4), a microbial dried-cell preparation dehydrated using acetone, as a catalyst for the asymmetric reduction of ketones for the first time and found that a number of ketones from aromatic ketones, β-keto esters, and simple aliphatic ketones are reduced to (*S*)-alcohols with >99% ee.[18] The properties and products of APG4, such as coenzyme dependence, alcohols for coenzyme regeneration, suitable buffers, optimum pH, optimum reaction temperature, stability, and preservability were examined, as well as the scope and limitations in regard to substrate specificity.

Results and Discussion

A. Preparations of the Enzyme (APG4). The crude alcohol dehydrogenase, the acetone powder of *Geotrichum candidum* IFO 4597 (APG4), was prepared as usual[17] by treating wet cells with acetone. The cultivation of *G. candidum* is very easy, requiring little technique, and the preparation of the acetone powder is also very simple (see Experimental Section). The simpleness of APG4 preparation is in striking contrast to the tediousness associated with isolation of an enzyme in a pure form.

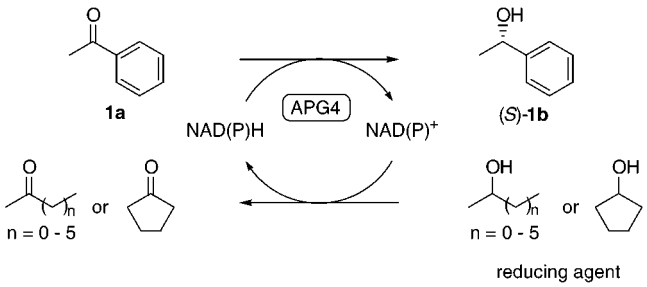
Table 1. Reduction of 1a[a] by *G. candidum*



catalyst	coenzyme[d]	reducing agent[e]	yield (%)[f]	ee (%)[f]	config[g]
whole cell[b]	none	none	52	28	*R*
APG4[c]	none	none	0		
APG4[c]	NAD^+	none	1	71	*S*
APG4[c]	none	2-propanol	8	98	*S*
APG4[c]	NAD^+	2-propanol	89	>99	*S*
APG4[c]	NADH	2-propanol	89	>99	*S*
APG4[c]	$NADP^+$	2-propanol	88	>99	*S*
APG4[c]	NADPH	2-propanol	83	>99	*S*
APG4[c]	NAD^+	cyclopentanol	97	>99	*S*
APG4[c]	$NADP^+$	cyclopentanol	86	>99	*S*

Reaction conditions: 20 h at 30 °C at 130 rpm in water (3 mL) for whole-cell reaction or in MES (2-(*N*-morpholino)ethanesulfonic acid) buffer (pH 7.0, 0.1 M, 3 mL) for APG4 reactions. [a] 0.08 mmol. [b] 0.5 g wet weight. [c] 10 mg. [d] 0.007 mmol. [e] 1.31 mmol. [f] Determined by GC analyses. [g] Determined by comparison of the GC retention times with those of authentic samples.

Scheme 1



B. Reaction Conditions for Asymmetric Reduction of Acetophenone (1a). The asymmetric reduction of acetophenone (**1a**) by *G. candidum* was investigated, and the results are shown in Table 1. The reduction of acetophenone (**1a**) catalyzed by the whole cell resulted in poor enantioselectivity (28% ee(*R*)). When the form of the catalyst was changed from wet whole-cell to dried powdered-cell (APG4), no reduction of **1a** was observed, which would indicate the loss of the necessary coenzyme(s) and/or coenzyme regeneration system(s) during the treatment of the cells with acetone. Addition of coenzyme, NAD^+, did not have a significant effect on the yield. Addition of 2-propanol resulted in only a small increase in the yield, but a significant improvement in the enantioselectivity was observed. Surprisingly, addition of both NAD^+ and 2-propanol largely enhanced both chemical yield and enantiomeric excess. Addition of NADH, $NADP^+$, or NADPH instead of NAD^+ and addition of cyclopentanol instead of 2-propanol also gave enantiomerically pure alcohol in high yield.

The reaction mechanism is shown in Scheme 1. When acetophenone (**1a**) is reduced to (*S*)-1-phenylethanol ((*S*)-**1b**), the reduced form of the coenzyme (NAD(P)H) is oxidized to $NAD(P)^+$, which is subjected to concomitant recycling to its reduced form by a reducing agent, such as 2-propanol or cyclopentanol. As the catalytic cycle is effective only for the reduction to the (*S*)-alcohol and does not involve any (*R*)-producing enzyme(s); the selectivity

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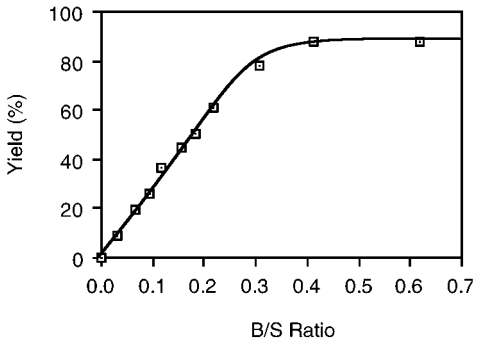

Figure 1. Effect of biocatalyst/substrate ratio (B/S Ratio) on the reduction of **1a**. Reaction Conditions: 20 h at 30 °C at 130 rpm in MES buffer (pH 7.0, 0.1 M, 3 mL); **1a**, 0.08 mmol; NAD^+, 0.007 mmol; 2-propanol, 1.31 mmol. Yields and ee were determined by GC analyses, and ee was >99%(*S*) for any amount of APG4 employed.

of the APG4 reduction system consisting of APG4, NAD(P)H, and a reducing agent is excellent, whereas the selectivity of the whole-cell reduction in which both (*S*)-enzyme(s) and (*R*)-enzyme(s) catalyze the reaction is low (28% ee(*R*)).

Ratio of Biocatalyst (APG4) to Substrate (B/S). The effect of the ratio of the biocatalyst (APG4) to the substrate (B/S) on the yield of reduction of acetophenone (**1a**) was investigated; it was found that a 0.4/1 B/S ratio was sufficient (Figure 1). One of the problems usually encountered in biocatalytic processes in organic synthesis is the requirement of an excessively high B/S ratios.[6b,c,19] For example, in the baker's yeast reduction of acetophenone (**1a**), a B/S ratio of 360/1 (1800 g of baker's yeast to reduce 5 g of **1a**) is necessary to obtain a 23% yield of (*S*)-1-phenylethanol ((*S*)-**1b**).[7a] When the whole cell of *G. candidum* was used to reduce **1a**, a B/S ratio of 50/1 is necessary.[15e] Moreover, the enantioselectivity of the reduction was not affected by the amount of the catalyst at all, and excellent selectivity (>99% ee) was obtained regardless of the B/S ratio.

Coenzymes. Unlike biotransformations using the whole cell, a coenzyme must be replaced in enzymatic transformations. Using 2-propanol as a reducing agent, the effectiveness of several nicotinamide coenzymes for the reduction of acetophenone (**1a**) was investigated. As shown in Table 1, NAD^+, NADH, $NADP^+$, and NADPH can be used to reduce **1a** with high yield. The selectivity of the reduction was hardly affected by the kind of coenzymes and remained very high (ee >99%). Next, the concentration effect of the NAD^+ on the yield of (*S*)-1-phenylethanol ((*S*)-**1b**) in the reduction of **1a** was studied, and it was found that only a small amount (0.025 mol equivalence to the substrate) is necessary to maximize the yield to 89%. The selectivity of the reduction also remained >99% ee even when only 0.0009 mol equivalence of NAD^+ was employed in the reduction. The concentration effects of NADH, $NADP^+$, and NADPH were also studied, and coenzyme concentration−yield profiles similar to that for NAD^+ were obtained.

Reducing Agents. The reduction catalyzed by APG4 does not proceed without a reducing agent even in the presence of a coenzyme as shown in Table 1. The use of glucose-6-phosphate,[11a,20] glucose,[11a,21] formate,[22] ethanol,[8] 2-propanol,[9−12,15b,e] 2-butanol,[13] *endo*-bicyclo[3.2.0]hept-2-en-6-ol,[14] 2-hexanol,[15e] and cyclopentanol[15c,15d,15e] to regenerate the reduced form of coenzymes, and FMN[23] and cyclohexanone[24] to regenerate the oxidized form of coenzymes have been reported. For the APG4 reduction system, the applicability of various alcohols as reducing agents in the reduction of acetophenone (**1a**) was investigated, and the results are shown in Table 2. Among the alcohols tested for their abilities as a reducing agent, 2-alkanols (2-propanol and racemic 2-pentanol) and cyclopentanol exhibited excellent results for both yield and ee.

Table 2. Effect of Alcohols as Reducing Agents on the Reduction of 1a†

reducing agent[a]	yield (%)[b]	ee (%)[b]	config[c]
2-propanol	89	>99	*S*
1-pentanol	9	94	*S*
2-pentanol	91	>99	*S*
3-pentanol	71	>99	*S*
cyclopentanol	96	>99	*S*
cyclohexanol	39	98	*S*
ethanol	8	98	*S*†

Reaction conditions: 20 h at 30 °C at 130 rpm in MES buffer (pH 7.0, 0.1 M, 3 mL): **1a**, 0.08 mmol; APG4, 10 mg; NAD^+, 0.007 mmol. [a] 1.31 mmol. [b] Determined by GC analyses. [c] Determined by comparison of the GC retention times with those of authentic samples.

Differences in effectiveness between cyclopentanol and cyclohexanol can be explained on the basis of the higher strain energy of cyclohexanone over that of cyclopentanone. The facile reduction of cyclohexanone compared with that of cyclopentanone was demonstrated in the relative rate (23:1) of the sodium borohydride reduction.[25] Cyclohexanone is easily reduced back to cyclohexanol competing with the reduction of the main substrate (**1a**), but cyclopentanone is reduced much slower in the undesired direction.

2-Alkanols from 2-propanol to 2-octanol and cyclopentanol were employed for further investigation to examine their concentration effects, which clarified that a large excess of the reducing agents is necessary to maximize the yield. The yield increased as the amount of the reducing agent was increased and reached around 90% when 15−20 equiv of the reducing agents to the substrate were used. All 2-alkanols afford similar correlations in the yield−mole equivalence relationship, whereas cyclopentanol worked a little better than 2-alkanols. An excess amount of the reducing agent is necessary to obtain the product in high chemical yields since the product, (*S*)-1-phenylethanol ((*S*) -**1b**), is oxidized back to acetophenone (**1a**) by the same enzyme(s) (see Scheme 1). Even with the excess amount of a reducing agent, the yield of the reaction does not reach 100% since increases in the yield stopped when the equilibrium between the desired reaction (reduction of acetophenone (**1a**)) and the undesired reverse reaction (oxidation of 1-phenylethanol (**1b**)) was reached. The undesired oxi-

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dation of 1-phenylethanol (**1b**) through a different route under aerobic conditions[24,26] also prevents the yield from becoming quantitative.

Although 2-alkanols from 2-propanol to 2-octanol and cyclopentanol were effective for the reduction system, from the synthetic point of view, the use of 2-propanol as a reducing agent is most advantageous due to its high volatility since a large amount of the remaining reducing agent has to be separated from the product during the workup.

Kinetic Parameters. Using APG4 homogenized with MES buffer (pH 7.0, 0.1 M), the initial rates of the reduction of acetophenone (**1a**) were measured as a function of the substrate concentration. The apparent kinetic parameters (K_m and V_{max}) were calculated via a Lineweaver−Burk plot to be 1.7 mM and 0.0085 mM·min^{-1}·mg^{-1} of APG4 for K_m and V_{max}, respectively.

Buffer. The effect of the buffer used in the reduction of acetophenone (**1a**) by APG4 on the reaction rate, yield, and ee was examined. It was found that various kinds of buffers (MES (2-(*N*-morpholino)ethanesulfonic acid−NaOH), KPB (potassium phosphate buffer), HEPES (4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid−NaOH), MOPSO (*β*-hydroxy-4-morpholinepropanesulfonic acid−NaOH), Tris (tris(hydroxymethyl)aminomethane−HCl), and Im (imidazole−HCl)) at pH 7.0 can be used for this reaction. Although the reaction rate depends slightly on the kind of buffer used, little effect on the yield was observed. Importantly, the enantioselectivity of the reduction remained very high (>99% ee) regardless of the kind of buffer. However, the buffer action must be present for the reaction to proceed because the reaction does not occur when ion exchanged water is used as a solvent.

pH. The effect of pH on the reaction rate, yield, and ee was also examined using MES buffer for pH between 4.5 and 7.7 and Tris buffer between 7.1 and 8.9. The optimum pH for the reduction of acetophenone (**1a**) by APG4 is around 8.5, although it proceeds within a wide pH range from 5.7 to higher than 8.9. The rate-limiting step of this reduction system is supposed to be the regeneration of the coenzyme from the oxidized form (NAD^+) to the reduced form (NADH) rather than the reduction of the acetophenone (**1a**) based on the optimum pH being 8.5 since the reduction of NAD^+ is faster in basic conditions than in acidic conditions. Interestingly, the reaction rate depends on the pH value, but the effect of pH on the yield is very small between a pH value of 6.4 and 8.9. The enantioselectivity of the reduction is not affected at all by the pH value between 5.7 and 8.9.

Reaction Temperature. The optimum reaction temperature was found to be 40 °C, whereas the reaction at 30 and 50 °C also proceeded smoothly, resulting in a high yield. However, at 60 °C, the reaction rate dropped to only one-third of the rate at the optimum reaction temperature. The stereoselectivity of the reduction was not influenced by the reaction temperature (>99% ee was obtained at 30, 40, 50, and 60 °C).

Thermostability. APG4 was incubated at various temperatures for 30 min at pH 7.0 and the residual activity was measured. APG4 was very stable at 30 °C in MES buffer and did not lose any activity. The activity of APG4 was retained at 94%, 82%, and 62% of the original after heating at 40, 50, and 60 °C for 30 min, respectively. However, most of the activity was lost with heating at 70 °C. The selectivity of the reduction was not influenced by incubation below 60 °C prior to the reaction and was maintained at >99% ee.

Preservability of biocatalysts is one of the most important factors in judging applicability of catalysts to organic synthesis. Accordingly, preservability of APG4 at 30 and −20 °C was investigated. Most of the activity of APG4 was retained after 48 h at 30 °C, and 69% and 35% were retained after 10 days and 22 days at 30 °C in air, respectively. Amazingly, the enzyme activities were still preserved to a certain extent even after the storage of APG4 for more than 45 days at 30 °C. APG4 can also endure long-term preservations in a refrigerator; 69% of the activity was preserved when the enzyme was stored at −20 °C for more than 2 years without special care. The enantioselectivity of the reduction remained very high (>99%) even with the enzyme being stored for 45 days at 30 °C or stored for 2 years at −20 °C. This proved that the observed stability and preservability of APG4 were remarkable.

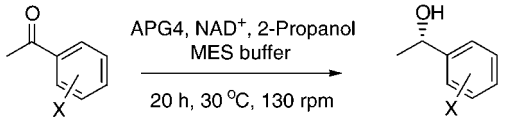
As a result of the thorough examination of the reaction conditions for APG4 reduction as well as the stability of APG4, the yield of the reaction changes only with a drastic change in the conditions, and the enantioselectivity remains very high (>99% ee) regardless of the reaction conditions. Similar experiments examining the reaction conditions for the APG4 reduction of *β*-keto esters were also conducted using ethyl 3-ketobutyrate or methyl 3-ketobutyrate as substrates. The yield was a little higher for the reduction of *β*-keto esters than that of acetophenone (**1a**), but analogous trends in the relationship between the yield and the conditions were observed. Enantioselectivity was also high for the reduction of *β*-keto esters regardless of the reduction conditions.

C. Synthetic Applications. The present reduction system has a great synthetic value due to the extremely wide substrate specificity; aromatic ketones, *β*-keto esters, and simple aliphatic ketones are reduced with excellent selectivity to the corresponding (*S*)-alcohols.

The high enantioselectivity of the APG4 reduction system was demonstrated by the reduction of acetophenone derivatives. Ortho-, meta-, or para-substituted fluoro, chloro, bromo, methyl, methoxy, and trifluoromethyl acetophenone (**2a**−**19a**) and pentafluoroacetophenone (**20a**) were reduced by the APG4 reduction system, and the results are listed in Table 3. An enantioselectivity of more than 99% ee was obtained for the reduction of all the acetophenone derivatives tested except that for *o*-(trifluoromethyl)acetophenone (**17a**) being 97% ee, while the yield of the reduction depends on the position of the substituent. Generally, the resulting alcohols were obtained in quantitative yields when there was a substituent at the ortho position. The yield of the meta-substituted acetophenone was slightly lower than that of ortho-substituted acetophenone, and a para substituent decreased the yield. This trend is not affected by the inductive effect of the substituent(s) since the fluoro or chloro substituents have the same effect on the yield as the methyl group. The plausible reason for the effect of the position of the substituent on the yield is that the yield is determined by the equilibrium between the reduction and undesired oxidation as described in the Reducing Agents section. It is known that this microbe

(26) Nakamura, K.; Matsuda, T.; Ohno, A. *Tetrahedron: Asymmetry* **1996**, *7*, 3021.

Table 3. Reduction of Aryl Methyl Ketones by APG4, NAD^+, and 2-Propanol



1a - 20a (*S*)-**1b** - (*S*)-**20b**

X	yield (%)[a,b]	ee (%)[a]	config[c]
H (**1**)	89 (74)	>99	*S*
o-F (**2**)	>99 (94)	>99	*S*
m-F (**3**)	95 (90)	>99	*S*
p-F (**4**)	74 (60)	>99	*S*
o-Cl (**5**)	>99 (94)	>99	*S*
m-Cl (**6**)	95 (91)	99	*S*
p-Cl (**7**)	62 (80)[d]	>99	*S*
o-Br (**8**)	97 (89)	>99	*S*
m-Br (**9**)	92 (85)	>99	*S*
p-Br (**10**)	95 (66)	>99	*S*
o-Me (**11**)	96 (73)	>99	*S*
m-Me (**12**)	86 (83)	>99	*S*
p-Me (**13**)	78 (70)	>99	*S*
o-MeO (**14**)	84 (85)[d]	>99	*S*
m-MeO (**15**)	90 (83)	>99	*S*
p-MeO (**16**)	29 (21)	>99	*S*
o-CF_3 (**17**)	6 (13)[d]	97	*S*
m-CF_3 (**18**)	96 (83)	>99	*S*
p-CF_3 (**19**)	73 (85)	>99	*S*
1′,2′,3′,4′,5′−F_5 (**20**)	62 (80)	>99	*S*

[a] Determined by GC analyses. [b] Isolated yield in parentheses. See Experimental Section for the reaction conditions. [c] Determined as described below. [d] Higher isolated yield was obtained than GC yield with more enzyme or coenzyme, longer reaction time, or the reaction under argon atmosphere. **1a** (120 mg, 1.0 mmol) was converted to (*S*)-**1b** (90 mg). GC conditions: CPCD 110 °C; *R*, 9.0 min; *S*, 9.7 min; $[\alpha]^{25}_D$ −55.1(*c* 1.63, $CHCl_3$) (lit.[33] $[\alpha]^{25}_D$ −57(*c* 5.12, $CHCl_3$), *S*). **2a** (1.11 g, 8.0 mmol) was converted to (*S*)-**2b** (1.06 g). GC conditions: CPCD 110 °C; *R*, 8.6 min; *S*, 9.2 min; $[\alpha]^{25}_D$ −44.5 (*c* 0.782, MeOH). The absolute configuration of this compound was tentatively assigned to be *S*. **3a** (1.11 g, 8.0 mmol) was converted to (*S*)-**3b** (1.01 g). GC conditions: CPCD 110 °C; *R*, 10.3 min; *S*, 11.1 min; $[\alpha]^{25}_D$ −33.5 (*c* 1.435, MeOH). The absolute configuration of this compound was tentatively assigned to be *S*. **4a** (360 mg, 2.6 mmol) was converted to (*S*)-**4b** (219 mg). GC conditions: CPCD 115 °C; *R*, 10.2 min; *S*, 11.0 min; $[\alpha]^{25}_D$ −37.7 (*c* 0.931, MeOH) (lit.[34] $[\alpha]^{31}_D$ −23.1 (*c* 3.12, MeOH), 70% ee(*S*)). **5a** (365 mg, 2.4 mmol) was converted to (*S*)-**5b** (346 mg). GC conditions: CPCD 130 °C; *R*, 11.1 min; *S*, 12.8 min; $[\alpha]^{25}_D$ −62.7 (*c* 0.894, $CHCl_3$) (lit.[29e] $[\alpha]_D$ −56.5 (*c* 0.0463, $CHCl_3$) 90% ee(*S*)). **6a** (154 mg, 1.0 mmol) was converted to (*S*)-**6b** (143 mg). GC conditions: CPCD 130 °C; *R*, 13.4 min; *S*, 14.2 min; $[\alpha]^{25}_D$ −43.5(*c* 1.08, $CHCl_3$) (lit.[35] $[\alpha]^{20}_D$ +36.7(*c* 1.0, $CHCl_3$) 84.6% ee(*R*)). **7a** (362 mg, 2.3 mmol) was converted to (*S*)-**7b** (293 mg). GC conditions: CPCD 130 °C; *R*, 14.0 min; *S*, 15.0 min; $[\alpha]^{25}_D$ −49.0 (*c* 1.84, ether) (lit.[29e] $[\alpha]_D$ −48.9 (*c* 0.0613, ether) 94% ee(*S*)). **8a** (2.6 g, 13 mmol) was converted to (*S*)-**8b** (2.3 g). GC conditions: CPCD 145 °C; *R*, 10.5 min; *S*, 12.4 min; $[\alpha]^{24}_D$ −54.6 (*c* 1.23, $CHCl_3$) (lit.[29e] $[\alpha]_D$ −50.5 (*c* 0.0305, $CHCl_3$) 94% ee(*S*)). **9a** (1.00 g, 5.0 mmol) was converted to (*S*)-**9b** (854 mg). GC conditions: CPCD 145 °C; *R*, 18.5 min; *S*, 19.3 min); $[\alpha]^{26}_D$ −28.6 (*c* 1.78, EtOH). The absolute configuration was determined to be *S* by debromination of **9b** to (*S*)-1-phenylethanol (see Experimental Section). **10a** (100 mg, 0.50 mmol) was converted to (*S*)-**10b** (67 mg). GC conditions: CPCD 150 °C; *R*, 10.5 min; *S*, 10.9 min; $[\alpha]^{23}_D$ −37.9 (*c* 1.13, $CHCl_3$) (lit.[29e] $[\alpha]_D$ −37.5(*c* 0.0666 $CHCl_3$) 96% ee(*S*)). **11a** (362 mg, 2.7 mmol) was converted to (*S*)-**11b** (269 mg). GC conditions: CPCD 130 °C; *R*, 7.1 min; *S*, 7.8 min; $[\alpha]^{25}_D$ −64.3 (*c* 1.04, EtOH) (lit.[29e] $[\alpha]_D$ −58.6 (*c* 0.0665, EtOH) 95% ee(*S*)). **12a** (309 mg, 2.3 mmol) was converted to (*S*)-**12b** (261 mg). GC conditions: CPCD 110 °C; *R*, 17.1 min, S: 18.3 min; $[\alpha]^{25}_D$ −39.8 (*c* 0.944, EtOH) (lit.[38] $[\alpha]^{15}_D$ −41.9 (*c* 0.500, EtOH) >99.9% ee(*S*)). **13a** (311 mg, 2.3 mmol) was converted to (*S*)-**13b**. Yield: 70% (220 mg). GC conditions: CPCD 105 °C; *R*, 15.6 min; *S*, 17.2 min; $[\alpha]^{26}_D$ −43.5 (*c* 0.994, MeOH) (lit.[34] $[\alpha]^{27}_D$ −22.3 (*c* 3.79, MeOH) 55% ee(*S*)). **14a** (557 mg, 3.7 mmol) was converted to (*S*)-**14b**. Yield: 85% (477 mg); ee >99% (*S*) (determined by GC analysis). GC conditions: CPCD 130 °C; *S*, 12.5 min; *R*, 13.4 min); $[\alpha]^{23}_D$ −63.0 (*c* 1.10, toluene) (lit.[35] $[\alpha]^{20}_D$ +48.9 (*c* 1.1, toluene) 81.5% ee(*R*)). **15a** (352 mg, 2.3 mmol) was converted to (*S*)-**15b** (296 mg). GC conditions: CPCD 130 °C; *R*, 15.6 min; *S*, 16.4 min); $[\alpha]^{22}_D$ −34.9 (*c* 0.849, MeOH) (lit.[36] $[\alpha]_D$ +35 (*c* 1, MeOH) 97% ee(*R*)). **16a** (704 mg, 4.7 mmol) was converted to (*S*)-**16b** (152 mg). GC conditions: CPCD 130 °C; *R*, 14.5 min; *S*, 15.8 min); $[\alpha]^{22}_D$ −51.9 (*c* 0.718, $CHCl_3$) (lit.[29e] $[\alpha]_D$ −46.2 (*c* 0.0273, $CHCl_3$) 87% ee(*S*)). **17a** (2.0 g, 11 mmol) was converted to (*S*)-**17b** (257 mg). GC conditions: CPCD 110 °C; *R*, 9.8 min; *S*, 10.8 min; $[\alpha]^{22}_D$ −45.5 (*c* 0.661, MeOH) (lit.[34] $[\alpha]^{22}_D$ −23.0 (*c* 1.26, MeOH) 55% ee(*S*)). **18a** (350 mg, 1.9 mmol) was converted to (*S*)-**18b** (294 mg). GC conditions: CPCD 120 °C; *R*, 8.2 min; *S*, 8.8 min; $[\alpha]^{22}_D$ −28.4 (*c* 1.26, MeOH) (lit.[34] $[\alpha]^{24}_D$ −17.1(*c* 2.92, MeOH) 59% ee(*S*)). **19a** (350 mg, 1.9 mmol) was converted to (*S*)-**19b** (299 mg). GC conditions: CPCD 120 °C; *R*, 10.1 min; *S*, 11.1 min; $[\alpha]^{22}_D$ −28.1 (*c* 1.13, MeOH) (lit.[29e] $[\alpha]^{21}_D$ −10.8 (*c* 0.0578, MeOH) 61% ee(*S*)). **20a** (281 mg, 1.3 mmol) was converted to (*S*)-**20b** (227 mg). GC conditions: CPCD 120 °C; *R*, 5.1 min; *S*, 5.6 min; $[\alpha]^{22}_D$ −6.33 (*c* 1.01, pentane) (lit.[37] $[\alpha]_D$ −8.1, (pentane), 97% ee(*S*)).

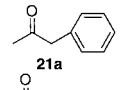
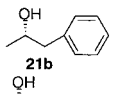
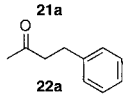
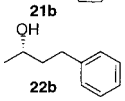
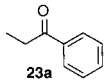
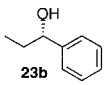
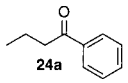
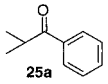
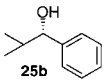
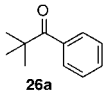
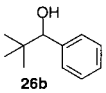
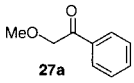
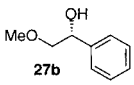
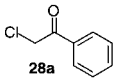
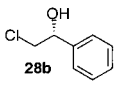
oxidizes para-substituted (*S*)-phenylethanol smoothly, but ortho-substituted phenylethanol is not oxidized at all[27] meaning the yield of the reduction increases in the order of para-, meta-, and ortho-substituted acetophenone.

The reduction on a gram scale proceeds smoothly without any loss in ee, and the isolation of the product alcohol with high yields was possible as illustrated in the reduction of *o*-bromoacetophenone (**8a**, 2.6 g) to (*S*)-1-(*o*-bromophenyl)ethanol ((*S*)-**8b**) giving an 89% yield (2.3 g, >99% ee). Importantly, any organic chemist will be able to reproduce this result because the high selectivity of this reduction system is very steady and independent of small changes in the experimental conditions such as scale of the reaction, pH, reaction temperature, etc.

Reduction by APG4 of several aromatic ketones having different length alkyl chains demonstrated the scope and limitations of the substrate specificity (Table 4). Phenyl moiety of acetophenone can be replaced by a benzyl (**21a**) or even by a 2-phenylethyl (**22a**) group with slightly better results of chemical yield than the reduction of acetophenone (**1a**) without a decrease in enantioselectivity. However, when the methyl moiety of acetophe-

(27) Nakamura, K.; Inoue, Y.; Matsuda, T.; Ohno, A. *Tetrahedron Lett.* **1995**, *36*, 6263.

Table 4. Reduction of Aromatic Ketones by APG4, NAD^+, and 2-Propanol

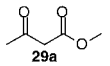
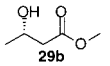
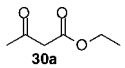
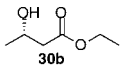
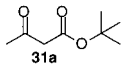
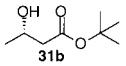
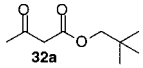
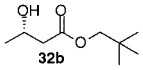
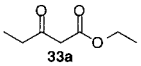
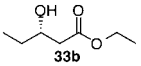
Substrate	Product	Yield(%)[a,b]	ee(%)[a]	Config.[c]
 **21a**	 **21b**	96(78)	>99	*S*
 **22a**	 **22b**	93(95)[d]	>99	*S*
 **23a**	 **23b**	41(25)	>99	*S*
 **24a**	no reaction	0	-	-
 **25a**	 **25b**	12(11)	99	*S*
 **26a**	 **26b**	1	-	-
 **27a**	 **27b**	8(5)	>99	*R*
 **28a**	 **28b**	80(49)	98	*R*

[a] Determined by GC, HPLC, or NMR analyses. The product was acetylated to determine ee for **21b**. [b] Isolated yield in parentheses. See Experimental Section for the reaction conditions. [c] Determined as described below. [d] Higher isolated yield was obtained than GC yield with more enzyme or coenzyme, longer reaction time, or the reaction under argon atmosphere. **21a** (367 mg, 2.7 mmol) was converted to (*S*)-**21b** (291 mg). GC conditions for 1-phenyl-2-propyl acetate: CPCD 110 °C; *S*, 13.7 min; *R*, 14.4 min; $[\alpha]^{25}_D$ +41.7 (*c* 1.19. $CHCl_3$) (lit.[38] $[\alpha]^{15}_D$ +39.7 (*c* 0.515, $CHCl_3$) >99.9% ee(*S*)). **22a** (350 mg, 2.4 mmol) was converted to (*S*)-**22b** (338 mg). GC conditions: CPCD 105 °C; *S*, 30.1 min; *R*, 31.6 min; $[\alpha]^{25}_D$ +21.0 (*c* 1.17, C_6H_6) (lit.[38] $[\alpha]^{22}_D$ +22 (*c* 0.380, C_6H_6) >99.9% ee(*S*)). **23a** (345 mg, 2.6 mmol) was converted to (*S*)-**23b** (86 mg). GC conditions: CPCD 110 °C; *R*, 15.5 min; *S*, 16.1 min; $[\alpha]^{25}_D$ −47.2 (*c* 0.643, $CHCl_3$) (lit.[29e] $[\alpha]_D$ −46.7 (*c* 0.0409, $CHCl_3$, 95% ee(*S*)). **25a** (1.00 g, 6.7 mmol) was converted to (*S*)-**25b** (113 mg). GC conditions: G-TA 95 °C; *R*, 29.9 min; *S*, 31.2 min; $[\alpha]^{26}_D$ −49.1 (*c* 0.828, ether) (lit.[29e] $[\alpha]_D$ −45.7 (*c* 0.0623, ether) 92% ee(*S*)). **27a** (2.0 g, 13 mmol) was converted to (*R*)-**27b** (99 mg). GC conditions: DEX 120 °C; *S*, 16.2 min; *R*, 17.2 min; $[\alpha]^{25}_D$ −40.2 (*c* 1.02, acetone) (lit.[39] $[\alpha]_D$ −34.4 (*c* 2, acetone) 76 ee(*R*)). **28a** (1.01 g, 6.5 mmol) was converted to (*R*)-**28b** (493 mg). HPLC conditions: OD 5:1 hexane−2-propanol, 0.5 mL/min; *S*, 15.6 min; *R*, 18.1 min; $[\alpha]^{25}_D$ −50.4 (*c* 1.78, cyclohexane) (lit.[40] $[\alpha]^{25}_D$ −48.1 (*c* 1.73, cyclohexane) 100% ee(*R*)).

none is replaced by an ethyl (**23a**), isopropyl (**25a**), or methoxymethyl (**27a**) group, the yield dramatically decreases, although the enantioselectivity remained high (>99% ee), and when the alkyl chain is elongated to a propyl (**24a**) or enlarged to a *tert*-butyl (**26a**) group, the reaction scarcely proceeds. α-Chloroacetophenone (**28a**) was also reduced by the APG4 system, and α-chloro-1-phenylethanol (**28b**) was obtained with 80% yield and 98% ee. This chiral alcohol can be converted to various compounds via epoxide.[28]

The versatility of the APG4 reduction system is further exemplified by the β-keto esters as substrates. The

Table 5. Reduction of β-Keto Esters by APG4, NAD^+, and 2-Propanol

Substrate	Product	Yield (%)[a,b]	ee(%)[a]	Config.[c]
 **29a**	 **29b**	>99	>99	*S*
 **30a**	 **30b**	>99(59)	>99	*S*
 **31a**	 **31b**	>99	>99	*S*
 **32a**	 **32b**	>99(74)	>99	*S*
 **33a**	 **33b**	72(52)	>99	*S*

[a] Determined by GC analyses. The product alcohol was acetylated to determined ee by GC analysis for **30b**, **32b**, and **33b**. [b] Isolated yield in parentheses. See Experimental Section for the reaction conditions. [c] Determined as described below. **29b** GC conditions: G-TA 90 °C; *S*, 7.0 min; *R*, 7.5 min. **30a** (136 mg, 1.0 mmol) was converted to (*S*)-**30b** (78 mg). GC conditions for ethyl 3-acetoxylbutanoate: G-TA, 85 °C; *R*, 19.2 min; *S*, 20.5 min; $[\alpha]^{25}_D$ +40.6 (*c* 1.09, $CHCl_3$) (lit.[41] $[\alpha]^{r.t.}_D$ +39.9 (*c* 1.8, $CHCl_3$) 92% ee(*S*)). **31b** GC conditions: DEX 90 °C; *S*, 12.5 min; *R*, 13.2 min. **32a** (172 mg, 1.0 mmol) was converted to (*S*)-**32b** (128 mg). GC conditions for 2,2-dimethylpropyl 3-acetoxylbutanoate: DEX, 115 °C; *S*, 10.8 min; *R*, 11.4 min); $[\alpha]^{25}_D$ +31.1 (*c* 1.01, $CHCl_3$) (lit.[42] $[\alpha]^{25}_D$ +26 (*c* 1.0, $CHCl_3$) 80% ee(*S*)). **33a** (500 mg, 3.5 mmol) was converted to (*S*)-**33b** (262 mg). GC conditions for ethyl 3-acetoxylpentanoate: G-TA, 110 °C; *R*, 8.7 min; *S*, 9.1 min; $[\alpha]^{26}_D$ +34.3 (*c* 1.05, $CHCl_3$) (lit.[41] $[\alpha]^{r.t.}_D$ +32.2 (*c* 5.1, $CHCl_3$) 93% ee(*S*)).

results of the reduction of 3-ketobutyrates (**29a**−**32a**) and a 3-ketopentanoate (**33a**) are shown in Table 5. 3-Ketobutyrates of methyl (**29a**), ethyl (**30a**), *tert*-butyl (**31a**), or neopentyl (**32a**) ester are reduced to (*S*)-hydroxyl esters (**29b**−**32b**) with >99% ee quantitatively. The yield and ee remained >99% regardless of the ester moiety. Ethyl 3-ketopentanoate (**33a**) can also be reduced to *S*-hydroxyl ester (**33b**) with >99% ee in 72% yield. The present reduction system is certainly suitable for the reduction of 3-ketobutyrates and 3-ketopentanoates.

Efficient catalysts for the enantioselective reduction of functionalized ketones have been reported,[29] but the asymmetric reduction of small aliphatic ketones remains a major challenge in organic chemistry.[9a] Simple aliphatic ketones from 2-octanone to 2-undecanone (**34a**−**37a**), 6-methyl-5-heptene-2-one (**38a**), and 5-chloro-2-pentanone (**39a**) were reduced by the APG4 system to the corresponding (*S*)-2-alkanols (**34b**−**39b**) giving high yields with 99% ee (Table 6). The present reduction system is beneficial for the reduction of aliphatic ketones over a nonenzymatic system by which, for example, in the reduction of 2-octanone (**34a**), 82% ee is the highest to the best of our knowledge.[30] Moreover, the reduction of 2-octanone (**34a**) gives only 24% ee for the product alcohol with BINAL-H, the well-known "super" catalyst

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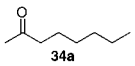
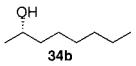
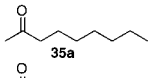
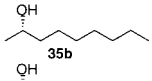
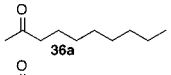
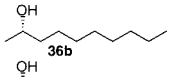
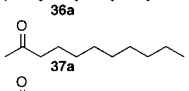
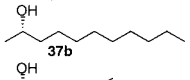
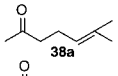
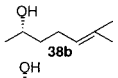
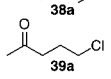
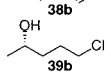
Table 6. Reduction of Aliphatic Ketones by APG4

Substrate	Product	Yield(%)[a,b]	ee(%)[c]	Config.[d]
 **34a**	 **34b**	87(62)	>99	*S*
 **35a**	 **35b**	87(77)	>99	*S*
 **36a**	 **36b**	85(49)	>99	*S*
 **37a**	 **37b**	60(61)[e]	>99	*S*
 **38a**	 **38b**	90(76)	99	*S*
 **39a**	 **39b**	92(40)	99	*S*

[a] Determined by GC analyses. [b] Isolated yield in parentheses. See Experimental Section for the reaction conditions. [c] Determined by GC analyses after acetylation of the product except for **38b**. [d] Determined as described below. [e] Higher isolated yield was obtained than GC yield with more enzyme or coenzyme, longer reaction time, or the reaction under argon atmosphere. **34a** (402 mg, 3.1 mmol) was converted to (*S*)-**34b** (252 mg). GC conditions for 2-octyl acetate: CPCD, 100 °C; *S*, 7.0 min; *R*, 7.8 min; $[\alpha]^{25}_D$ +9.00 (*c* 1.23, $CHCl_3$) (lit.[9a] $[\alpha]_D$ +8.78 ($CHCl_3$) 97% ee(*S*)). **35a** (399 mg, 2.8 mmol) was converted to (*S*)-**35b** (313 mg). GC conditions for 2-nonyl acetate: CPCD 110 °C; *S*, 8.1 min; *R*, 8.7 min; $[\alpha]^{25}_D$ +8.66 (*c* 1.18, $CHCl_3$) (lit.[9a] $[\alpha]_D$ +7.96 ($CHCl_3$) 98% ee(*S*)). **36a** (209 mg, 1.3 mmol) was converted to (*S*)-**36b** (103 mg). GC conditions for 2-decyl acetate: CPCD 125 °C; *S*, 7.8 min; *R*, 8.4 min); $[\alpha]^{23}_D$ +10.3 (*c* 0.80, EtOH) (lit.[43] $[\alpha]^{25}_D$ +4.22 (*c* 6.28, EtOH) 83.0% ee(*S*)). **37a** (450 mg, 2.6 mmol) was converted to (*S*)-**37b** (276 mg). GC conditions for 2-undecyl acetate: CPCD 130 °C; *S*, 10.7 min; *R*, 11.4 min); $[\alpha]^{21}_D$ +7.92 (*c* 0.75, EtOH). The absolute configuration of this compound was determined to be *S* by comparison of the optical rotation with that of the authentic sample synthesized. **38a** (397 mg, 3.2 mmol) was converted to (*S*)-**38b** (306 mg). GC conditions: G-TA 85 °C; *S*, 7.3 min; *R*, 7.8 min; $[\alpha]^{25}_D$ +12.0 (*c* 2.93, $CHCl_3$) (lit.[9a] $[\alpha]_D$ +10.76 ($CHCl_3$) 99% ee(*S*)). **39a** (612 mg, 5.1 mmol) was converted to (*S*)-**39b** (249 mg). GC conditions for 5-chloro-2-pentyl acetate: DEX 110 °C; *S*, 5.3 min; *R*, 6.2 min; $[\alpha]^{26}_D$ +14.9 (*c* 1.19, $CHCl_3$) (lit.[9a] $[\alpha]_D$ +15.58 ($CHCl_3$) 98% ee(*S*)).

for hydrogenolysis.[29b] In contrast to these low selectivities, the reduction of 2-octanone (**34a**) by this present APG4 system affords (*S*)-alcohol (**34b**) with >99% ee.

This system can also reduce aliphatic ketones with functional groups such as olefin or chloride giving a high yield with 99% ee. For example, the reduction of 6-methyl-5-heptene-2-one (**38a**) by the APG4 system proceeded smoothly and afforded (*S*)-(+)-sulcatol (**39b**), the aggregation pheromone produced by males of *Gnathotrichus sulcatus*,[31] in one step. The reduction of 5-chloro-2-pentanone (**39a**) was also successful and afforded (*S*)-5-chloro-2-pentanol (**39b**) giving high yields with 99% ee. This chiral alcohol is an excellent bifunctional building block that may be conveniently employed for synthesis of natural products containing chiral carbinol centers.[9b] For example, (*S*)-**39b** is used as a chiral building block for the total synthesis of (+)-(*S*,*S*)-(*cis*-6-methyltetrahydropyran-2-yl)acetic acid,[9b] a naturally occurring heterocycle that has been isolated from the perfume material civet, a glandular secretion of the civet cat (Viverra civetta).[32]

Determination of Absolute Configurations. The absolute configuration of 1-(*m*-bromophenyl)ethanol (**9b**) was determined by conversion to optically active 1-phenylethanol (**1b**) by Pd/H_2 and comparison of the sign of optical rotation with that of the literature value.[33] The absolute configuration of 2-undecanol (**37b**) was determined by synthesizing the authentic (*S*)-**37b** from (*S*)-propylene oxide.

Conclusions

A simple reagent for asymmetric reduction of various kinds of ketones for use by organic chemists with a little background in biochemistry or microbiology has been created. The use of the acetone powder of the microbe eliminates the laborious isolation of the enzyme and problems of low selectivity associated with catalysis by the whole cell. To investigate the substrate specificity, a wide variety of ketones was subjected to the APG4 reduction system. The substrate specificity of the acetone powder system is very wide, and excellent enantioselectivity of the reduction was obtained for most of the wide variety of substrates. Since the yield of the reduction is also satisfactory, the present method is highly effective for asymmetric synthesis of optically pure aromatic alcohols, aliphatic alcohols, and hydroxy esters.

Experimental Section

Instruments. Gas chromatographic analyses were performed using chiral GC-columns (Chiraldex G-TA; 40 or 30 m; He 2 mL/min (G-TA), CP-cyclodextrin-B-2,3,6-M-19; 25 m; He 2 mL/min (CPCD), Chirasil-DEX CB; 25 m; He 2 mL/min (DEX)). HPLC analyses were performed using Chiralcel OD (0.46 cm × 25 cm (OD)).

Preparations of the Enzyme (APG4). Cultivation of *Geotrichum candidum*. Glycerol (30 g), yeast extract (10 g), polypeptone (5 g), KH_2PO_4 (11.18 g), and K_2HPO_4 (3.12 g) were mixed with water and the volume was adjusted to 1.0 L with water. A portion of the resulting solution (30 mL) was placed in an 100-mL test tube, and the rest was placed in a 2-L Erlenmeyer flask, which were covered with silicone caps and sterilized (121 °C, 20 min). The solution in the test tube was inoculated with the stored microbe of *G. candidum* IFO 4597 and stirred for 24 h at 30 °C at 130 rpm. The resulting mixture in the test tube was transferred to the flask and stirred for 24 h at 30 °C at 130 rpm. The resulting mixture was filtered to obtain the cells (18 g wet weight (wet wt)).

Preparation of Acetone Powder (APG4). The cells of *G. candidum* IFO 4597 (18 g wet wt) were mixed with cold acetone (−20 °C, 150 mL), and the cells were collected by filtration. The procedure was repeated five times, and then the cells were dried under reduced pressure. The dried cells (3.8 g) were obtained and used without further purification.

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Whole-Cell Reduction of Acetophenone (1a). Acetophenone (**1a**) (0.08 mmol) was added to a suspension of freshly prepared whole cells (0.5 g wet wt) in water (3 mL) and shaken at 130 rpm at 30 °C for 20 h. The resulting mixture was put on Extrelut (Merck) and eluted with ether. The chemical yield and ee of 1-phenylethanol (**1b**) were determined by GC analysis of the ether extract to be 52% and 28%, respectively (GC conditions: CPCD, 110 °C).

APG4 Reduction of Ketones. A ketone (0.08 mmol), NAD^+ (0.007 mmol), and 2-propanol (1.31 mmol) were added to a suspension of APG4 (10 mg) in MES (2-(*N*-morpholino)-ethanesulfonic acid) buffer (pH 7.0, 0.1 M, 3 mL). The mixture was shaken at 130 rpm at 30 °C for 20 h, and the resulting mixture was put on Extrelut and eluted with ether. Chemical yield and ee of the product were determined by GC analysis, HPLC analysis, or NMR analysis of the ether extract. A similar experiment was conducted using NADH, $NADP^+$, and NADPH as a coenzyme and cyclopentanol and 2-alkanols from 2-propanol to 2-octanol as a reducing agent.

Synthetic Applications. Preparation of 1-Phenyl-2-propanone (21a). This ketone was prepared through the oxidation of 1-phenyl-2-propanol (22 mmol, 3.0 g) by stirring in DMSO (300 mL), DCC (132 mmol, 25 g), and trifluoroacetic acid (33 mmol, 3.8 g) under an atmosphere of argon at room temperature for 4 days. Yield 39% (1.2 g); ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 7.17−7.35 (m, 5H, Ph); IR (neat) 700, 737, 1030, 1078, 1159, 1229, 1358, 1422, 1454, 1497, 1603, 1713, 2926, 3030, 3063 cm^{-1}.

General Procedure for the Reduction of Ketones in Preparative Scale. A ketone (1.6 mmol), 2-propanol (26 mmol, 2.0 mL), NAD^+ (100 mg). and APG4 (200 mg) were added to 60 mL of MES buffer (0.1 M, pH 7.0). The mixture was stirred at 30 °C for 20 h at 130 rpm under an argon atmosphere and filtered through Extrelut, which was washed with ether. The filtrate was extracted with ether, and the combined ether solution was washed with water, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (eluent 5:1 to 3:1 hexane−ethyl acetate) followed by distillation with a Kugelrohr apparatus. The product was identified with ^{1}H NMR, IR, and elemental analysis. Ee was determined by GC analysis or HPLC analysis. An absolute configuration was assigned on the basis of the literature values of optical rotation, unless otherwise noted.

Determination of Absolute Configurations. (*S*)-1-Phenylethanol (1b) from Chiral (*m*-Bromophenyl)ethanol (9b) Obtained by APG4 Reduction of *m*-Bromoacetophenone (9a). Chiral *m*-(bromophenyl)ethanol (**9b**) (137 mg, 0.68 mmol) obtained by APG4 reduction of *m*-bromoacetophenone (**9a**), ethanol (13 mL), sodium hydroxide (400 mg), and 5% palladium on carbon (45 mg) was stirred overnight under an atmosphere of hydrogen at room temperature. The catalyst was removed by filtration, and the filtrate was neutralized with 1 N HCl. Brine was added to the mixture, and the entire mixture was extracted with ether. The combined extracts were washed with water, aqueous sodium bicarbonate, and water and dried over Na_2SO_4, and the solvent was evaporated. The residue was purified by silica gel column chromatography (eluent 4:1 hexane−ethyl acetate) followed by distillation with a Kugelrohr apparatus. The ^{1}H NMR spectrum of the product was identical with that of 1-phenylethanol. Ee of the product was determined to be 88% by GC analysis (GC conditions: CPCD, 110 °C): yield 64% (53 mg); $[\alpha]^{25}_D$ −46.8 (*c* 1.17, $CHCl_3$) (lit.[33] $[\alpha]^{25}_D$ −57 (*c* 5.12, $CHCl_3$) *S*).

(*S*)-2-Undecanol from (*S*)-Propylene Oxide. CuI (0.2 mmol, 40 mg) and Me_2S (0.2 mL) were added to a cold (−20 °C) solution of *n*-octylmagnesium bromide (0.93 M in THF, 2.4 mL) under an atmosphere of argon. Then, a THF (2 mL) solution of (*S*)-propene oxide (116 mg, 2 mmol) was added dropwise to the mixture, and the mixture was stirred for 2 h at the same temperature. The reaction was quenched by aqueous NH_4Cl, the mixture was acidified with 1 N HCl, and the product was extracted with ether. The combined ether extracts were washed with water, aqueous sodium bicarbonate, and water and dried over anhydrous Na_2SO_4, and the solvent was evaporated. The crude product was purified by silica gel column chromatography (eluent 8:1 to 5:1 hexane−ethyl acetate) followed by distillation with a Kugelrohr apparatus. The NMR spectrum of the product was identical with that of 2-undecanol: yield 70% (240 mg); $[\alpha]^{25}_D$ +7.44 (*c* 1.27, EtOH). The product was acetylated with acetyl chloride and pyridine in CH_2Cl_2 to determine ee by GC analysis (GC conditions: CPCD, 120 °C); ee 99%.

Acknowledgment. This work was supported by Nagase Science and Technology Foundation and by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture of Japan.

Supporting Information Available: ^{1}H NMR spectral, IR spectral, and elemental analysis data of chiral alcohols (**1b**−**23b, 25b, 27b, 28b, 30b, 32b**−**39b**) (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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