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Chemoenzymatic Synthesis of Optically Active 2-Phenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile

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Abstract—(±)-2-Cyano-2-phenyl-1-hexanol **3** was resolved to each enantiomer using *Candida rugosa* and *Pseudomonas fluorescens* lipases in 62 and 99% ee, respectively. The absolute stereochemistry of one of the enantiomers was determined to be (*S*) by diastereomeric amide formation and X-ray crystallography. The resolved alcohols of (*R*)- and (*S*)-isomer were transformed to Systhane® analogues.

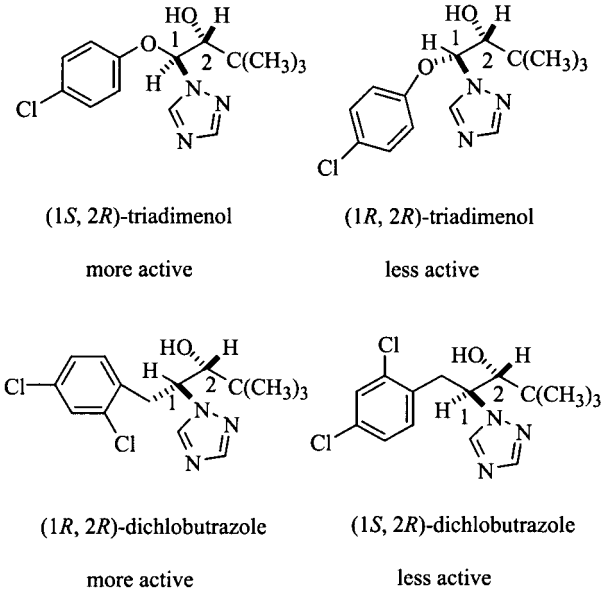

Figure 1. Diastereomeric pairs biological activity.

2-*p*-Chlorophenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile **1** (Systhane®) is a systemic fungicide which inhibits ergosterol biosynthesis.[1] The stereochemistry of the sterol biosynthesis inhibitors, particularly of the azoles and amines, can often have a decisive influence upon biological activity. The question concerning the influence of stereochemistry upon biological activity is therefore of particular interest in this class. For fungicidal examples, with triadimenol the biological activity of the *threo* diastereomer is higher than that of the *erythro* diastereomer.[2] In the case of dichlobutrazole, the enantiomers (1*R*, 2*R*) and (1*S*, 2*S*) are much more active than their diastereomers (1*S*, 2*R*) and (1*R*, 2*S*) in an S_8 yeast enzyme system (Fig. 1).[3]

Systhane® **1** is commercially available for crop protection as a racemate and has one quaternary chiral carbon. To date, there are no reports that resolve it to a single isomer and compare the biological activities between the two enantiomers. Thus we do not know which enantiomer is more active biologically. We have been interested in compound **1** with a view to separating the two enantiomers and testing their biological activities. To resolve them, we

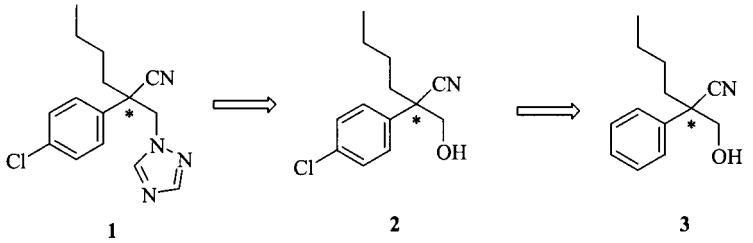

Figure 2. Retrosynthesis of Systhane®.

Keywords: chemoenzymatic; fungicide; quaternary carbon; lipase-catalyzed reaction.
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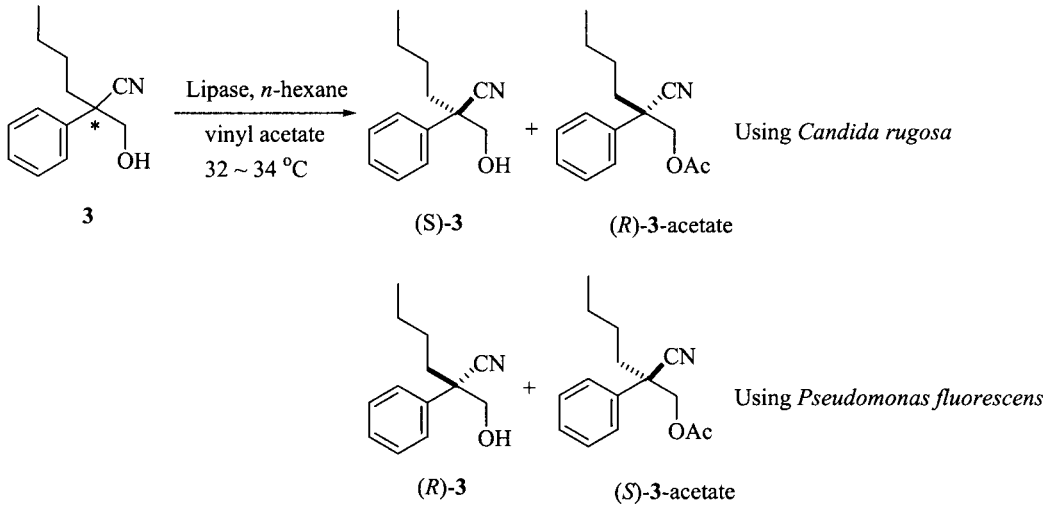


Scheme 1. Lipase-catalyzed reaction of compound **3**.

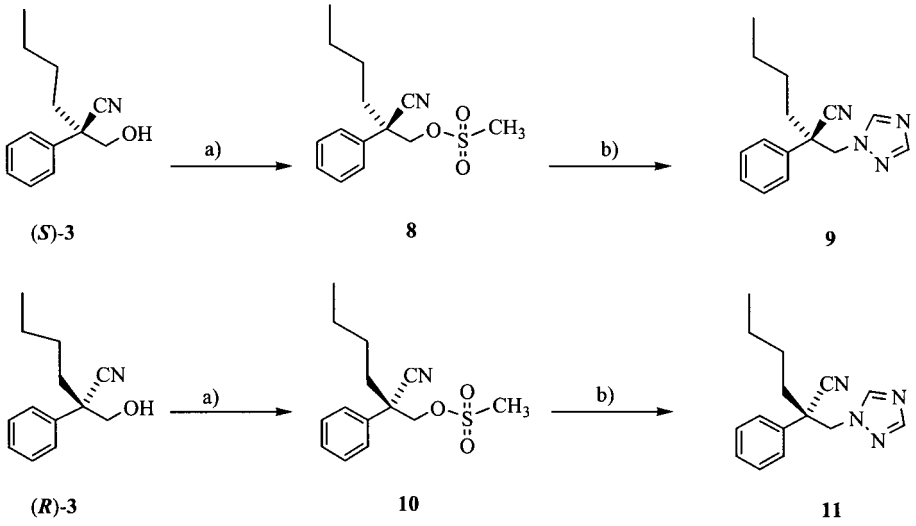
used lipase which is a useful catalyst for the preparation of enantiomerically pure compounds[4] (Fig. 2).

In a lipase-catalyzed reaction, it is important to select a proper substrate. By screening several lipases for resolving compound **2**, we did not find promising ones. Thus we synthesized compound **3** as the intermediate for the preparation of compound **1**. It can be transformed to compound **1** and other related compounds by chemical modifications such as aromatic chlorination, nitration and alkylation. We selected two kinds of lipase, *Pseudomonas fluorescens* and *Candida rugosa* which resolved them moderately. We report here the results of the resolution and structural determination of compound **3** (Scheme 1).

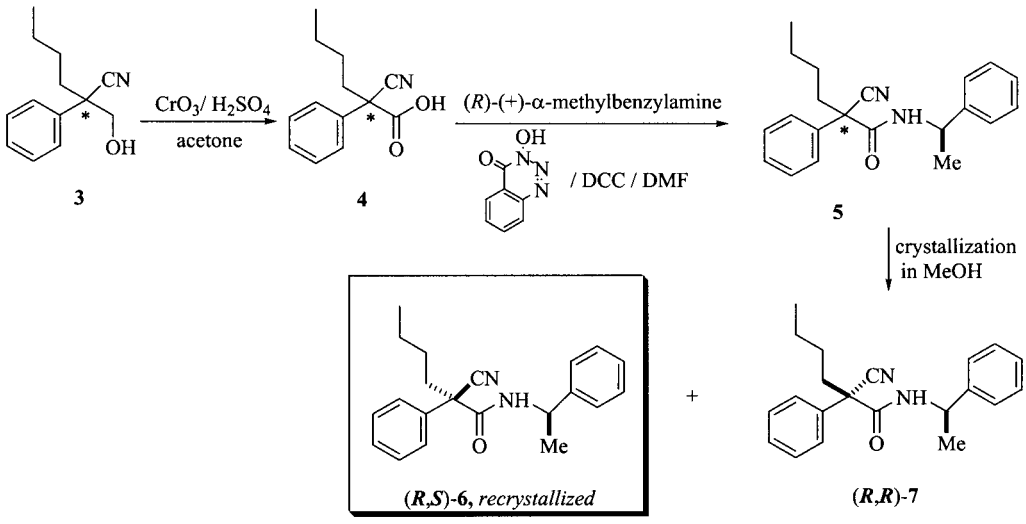
Table 1. Resolutions of compound **3** using *Candida rugosa* and *Pseudomonas fluorescens*

Lipase	Reaction time (h)	Conversion (%)	Ee (%)		*E*
			Alcohol	Acetate	
Candida rugosa (CRL)	1	30	26 (*S*)	62 (*R*)	5.5
Pseudomonas fluorescens (PFL)[a]	24	40	50 (*R*)	76 (*S*)	11
Pseudomonas fluorescens (Amano AK)[b]	48	22	28 (*R*)	99 (*S*)	>200

[a] *Pseudomonas fluorescens* lipase from Aldrich Co.
[b] *Pseudomonas fluorescens* lipase from Amano Pharmaceutical Co.



Scheme 2. Synthesis of compounds **9** and **11**.



Scheme 3. Synthesis of *N*-[(*R*)-α-methylbenzyl]-(2*S*)-cyano-2-phenylhexanamide **6**.

Compound **3** was prepared by conventional methods.[5] We resolved it using *C. rugosa* and *P. fluorescens* lipases because of their effectiveness among several lipases in the previous report.[6] The reaction was proceeded by transesterification of the substrate with vinyl acetate in the presence of lipase at 32–34°C and the solvent was *n*-hexane.[7] As shown in Table 1, the faster reacting enantiomer with *C. rugosa* and *P. fluorescens* lipase was found to be (*R*) and (*S*)-one, respectively. Surprisingly, the resolving efficiency between two kinds of *P. fluorescens* lipase was different although they are derived from the same species.

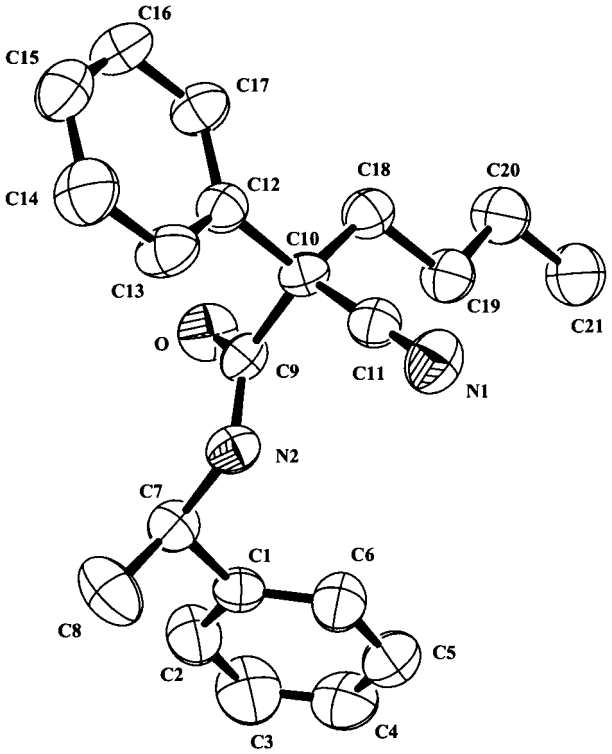


Figure 3. Molecular structure of *N*-[(*R*)-α-methyl benzyl]-(2*S*)-2-cyano-2-phenylhexanamide **6**.

But the faster reacting enantiomer was the same as (*S*)-enantiomer. The enantioselectivity (*E*)[8] using *P. fluorescens* lipase from Amano Pharmaceutical Co. was up to 200 and we could obtain the enantiomerically pure (*S*)-enantiomer. When *C. rugosa* lipase was used, we got the (*R*)-enantiomer in 62% ee. Thus we adopted a strategy such as product recycling[9] to enhance its ee value. Two further enzymatic resolutions of the compound **3** derived from the first resolved (*R*)-acetate produced the (*R*)-enantiomer in up to 99% ee. Each enantiomer was mesylated and displaced by triazole sodium salt by the general method as described in Scheme 2.

Next, we attempted to crystallize diastereomeric derivatives as follows: (i) esterification of the alcohol **3** with (1*R*)-(−)-camphorsulfonyl chloride and (*S*)-(+)-mandelic acid, respectively; (ii) esterification of the acid **4** with alcohols such as (−)-menthol and (+)-cinchonine; (iii) diastereomeric salts of the acid **4** with l-quinine. All of the trials failed to crystallize the diastereomeric derivatives for determining the absolute stereochemistry of compound **3**. Thus we derivatized carboxylic acid **4** to its diastereomeric amide as described in Scheme 3. The diastereomeric amide of (±)-acid **4** and (*R*)-(+)-α-methylbenzylamine easily crystallized in methanol and one of the diastereomeric pairs was submitted to X-ray crystallographic analysis. Its absolute stereochemistry was the (1*R*,2*S*)-amide **6**. It was identical to the amide which resulted from the reaction of (*R*)-(+)-α-methylbenzylamine with the acid of the (*S*)-alcohol **3**, which was resolved by *C. rugosa* lipase. From these results, we determined the stereochemistry of each enantiomer derived from compound **3**.

In summary, (±)-2-cyano-2-phenyl-1-hexanol **3** was resolved to (*S*)-enantiomer with up to 99% ee using *P. fluorescens* lipase (Amano AK) and to (*R*)-enantiomer with up to 98% ee by three times recycling enzymatic reactions using *C. rugosa* lipase. The absolute stereochemistry of each enantiomer was determined by X-ray crystallography (Fig. 3).

Each enantiomer of the Systhane® analogue (phenyl without

chloride) was synthesized and submitted to testing for fungicidal activities of both enantiomers. We will continue to synthesize Systhane® by chlorination of each enantiomer of the aromatic compound **3** and study the differences of biological activity between them. Furthermore, after synthesizing other related analogues, we will study the different biological activities between each enantiomer.

Experimental

General

^{1}H NMR (250 or 300 MHz) and ^{13}C NMR spectra (63 or 75 MHz) were recorded on a Varian Gemini 250 or 300 MHz spectrometer with TMS as an internal reference. IR spectra were recorded on a MIDAC 101025 FT-IR spectrometer and optical rotation was measured on Autopol® III polarimeter (Rudolph Research Co.). Low EI resolution mass spectra were determined on HP GC 5972 [Column: Hewlett-Packard fused silica capillary column HP-5 cross-linked 5% Phenyl methyl silicone, Column ID 0.20 mm, Film thickness: 0.11 μm, Length: 25 m, Detector: Mass selective detector, 280°C, Injector 280°C, Program: Ini. temp. 70°C (2 min), 20°C/min, Final temp. 300°C (20 min)] and HP MS 5988A system at 70 eV. Analytical chiral GLC work was carried out on a Hewlett Packard 5890 Series II Gas Chromatograph [Column: Beta-DEX™ 110, Fused silica capillary column, Column ID 0.25 mm, Film thickness: 0.25 μm, Length: 30 m, Detector: FID 250°C, Injector 250°C, Program: Ini. temp. 140°C (40 min), 2°C/min, Final temp. 200°C (10 min)].

Materials

All reactions were carried out under an atmosphere of nitrogen. Column chromatography was performed on Merck Silica Gel 60 (230–400 mesh). TLC was carried out using glass sheets precoated with silica gel 60 F_{254} prepared by E. Merck. All the commercially available reagents were obtained from Aldrich, Fluka and Tokyo Kasei Chemical Company, and generally used without further purification. Solvents were distilled over appropriate drying materials before use. Lipase AK (*P. fluorescens*, >20000 u/g) was obtained from Amano Pharmaceutical Company. CRL (*C. rugosa*, 860 u/mg) and PFL (*P. fluorescens*, 42.5 u/mg) were obtained from Sigma and Aldrich Company, respectively.

Synthesis of (±)-2-cyano-2-phenyl-1-hexanol (3).[5] To a stirred suspension of sodium hydride (6.1 g, 170 mmol, 60% dispersion in mineral oil) in dry DMF (100 mL) was added dropwise benzyl cyanide (17.6 g, 150 mmol) for 30 min at 0°C. After the mixture was stirred for 30 min, 1-bromobutane (20.5 g, 150 mmol) was added at 15°C for 12 h. The reaction medium was quenched with cold ice water (200 mL) and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated to furnish 30 g of crude 1-cyano-1-phenylpentane. Silica gel column chromatography (*n*-hexane/ethyl acetate, 10:1) provided 21.3 g (82%) of 1-cyano-1-phenylpentane as a clear oil. R_f 0.33 (*n*-hexane/ethyl acetate, 9:1); GC/MSD retention time (min) 7.24, (*m*/*z*) 51, 57, 65, 77, 89, 103, 117 (100), 130, 145, 158, 173 (M^+); IR (neat) 3120, 2958, 2240, 1456, 1380 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.90 (t, J=8.5 Hz, 3H), 1.33–1.47 (m, 4H), 1.86–1.97 (m, 2H), 3.76 (dd, J=8.0, 10.0 Hz, 1H), 7.28–7.40 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.1, 22.5, 29.5, 36.0, 37.8, 121.3, 127.6, 128.3, 129.4, 136.4; Anal. Calcd for $C_{12}H_{15}N$: C, 83.19; H, 8.73; N, 8.08. Found: C, 83.15; H, 8.75; N, 8.03.

To a stirred suspension of sodium hydride (5.82 g, 145 mmol, 60% dispersion in mineral oil) in dry DMF (150 mL) was added dropwise 1-cyano-1-phenylpentane (21.0 g, 121 mmol) for 30 min at 0°C, paraformaldehyde (8 g, 5 equiv.) was added in several portions at 0°C. After the complete addition, the mixture was warmed to room temperature and stirred overnight. The reaction medium was quenched with cold ice water (300 mL) and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated to furnish 26.5 g of crude **3**. Silica gel column chromatography (*n*-hexane/ethyl acetate, 4:1) provided 21.0 g (85.4%) as a clear oil. R_f 0.56 (*n*-hexane/ethyl acetate, 2:1); GC/MSD retention time (min) 8.80, (*m*/*z*) 51, 63, 77, 91, 103, 117, 130, 145, 158, 173 (100), 184 (M^+-18); IR (neat) 3502, 3122, 2958, 2240, 1456, 1381, 1064 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86 (t, J=8.6 Hz, 3H), 1.10–1.59 (m, 4H), 1.80–2.15 (m, 2H), 1.91 (br s, 1H), 3.89 (s, 2H), 7.34–7.46 (m, 5H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 14.1, 23.0, 27.4, 35.7, 51.5, 69.8, 122.0, 126.8, 128.6, 129.5, 136.2; Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.65; H, 8.47; N, 6.85.

Synthesis of acetate of (±)-2-cyano-2-phenyl-1-hexanol (3). To a solution of (±)-**3** (4.4 g, 21.7 mmol) in anhydrous methylene chloride (20 mL) was added a trace of 4-(dimethylamino)pyridine as catalyst, excess pyridine (5 mL) and acetic anhydride (10 mL). After the mixture was stirred for 2 h at room temperature, and poured into cold 10% aqueous HCl solution (30 mL), and extracted with diethyl ether (2×20 mL). The combined organic extracts were washed saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated to furnish 5.1 g of crude acetyl ester. Silica gel column chromatography (*n*-hexane/ethyl acetate, 10:1) provided 4.94 g (93%) of (±)-2-cyano-2-phenylhexyl acetate as a clear oil. R_f 0.38 (*n*-hexane/ethyl acetate, 4:1); GC/MSD retention time (min) 9.23, (*m*/*z*) 51, 63, 77, 91, 103, 166, 130, 145, 158, 173 (100), 186, 215, 245 (M^+); IR (neat) 3120, 2958, 2242, 1748, 1454, 1380, 1224, 1048 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.86 (t, J=8.8 Hz, 3H), 1.12–1.50 (m, 4H), 1.8–1.95 (m, 2H), 2.06 (s, 3H), 4.36 (s, 2H), 7.33–7.45(m, 5H); ^{13}H NMR (63 MHz, $CDCl_3$) δ 13.5, 20.3, 22.2, 26.6, 35.8, 47.8, 68.3, 120.4, 126.0, 128.1, 128.5, 135.1, 169.9; Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.42; H, 7.81; N, 5.58.

Kinetic resolution of (±)-2-cyano-2-phenyl-1-hexanol (3) using *P. fluorescens* lipase (Amano AK)

To a stirred solution of compound **3** (210 mg, 1.03 mmol) in

anhydrous *n*-hexane/ethyl acetate (9:1, 10 mL) was added Amano AK (210 mg) and vinyl acetate (89 mg, 1.03 mmol) at 32–34°C. After stirring for 48 h, GC analysis showed a conversion of 22%. From the reaction mixture, the enzyme was removed by filtration and washed with diethyl ether (3×10 mL). The combined organic layer was concentrated to afford an oily residue, which was chromatographed on silica-gel column with *n*-hexane/ethyl acetate (4:1) to give the acetate of (*S*)-**3** and unreacted alcohol (*R*)-**3**. The isolated acetate of (*S*)-**3** was hydrolyzed with 1.2N methanolic KOH solution to afford the corresponding alcohol (*S*)-**3**. $[\alpha]_D^{26}=-11.02$ (*c* 0.58, methanol). Retention time (min) of (*S*)-(−)-**3** was 54.88 from Beta DEX™ chiral column. The enantiomeric excess of reacted alcohol (*S*)-**3** and unreacted alcohol (*R*)-**3** were 99 and 28%, respectively.

Kinetic resolution of (±)-2-cyano-2-phenyl-1-hexanol (3) using *P. fluorescens* lipase (PFL)

To a stirred solution of compound **3** (210 mg, 1.03 mmol) in anhydrous *n*-hexane/ethyl acetate (9:1, 10 mL) was added PFL (210 mg) and vinyl acetate (89 mg, 1.03 mmol) at 32–34°C. After stirring for 24 h, GC analysis showed a conversion of 40%. By the same procedure as above, the enantiomeric excess of reacted alcohol (*S*)-**3** and unreacted alcohol (*R*)-**3** were obtained in 76 and 50%, respectively.

Kinetic resolution of (±)-2-cyano-2-phenyl-1-hexanol (3) using *C. rugosa* lipase (CRL)

To a stirred solution of compound **3** (102 mg, 0.50 mmol) in anhydrous *n*-hexane/ethyl acetate (9:1, 10 mL) was added CRL (100 mg) and vinyl acetate (43 mg, 0.50 mmol) at 32–34°C. After stirring for 1 h, GC analysis showed a conversion of 30%. By the same procedure as above, the enantiomeric excess of reacted alcohol (*R*)-**3** and unreacted alcohol (*S*)-**3** were obtained in 62 and 26%, respectively.

Product recycling using *C. rugosa* lipase (CRL)

The first resolved alcohol (*R*)-**3** was used for enzyme reaction using the same lipase under the above condition. The (*R*)-enantiomer was obtained in 62% ee and by third recycling, it was up to 98% ee. $[\alpha]_D^{26}=+11.05$ (*c* 0.58, methanol), retention time (min) of (*R*)-(+)-**3** was 54.21 from Beta DEX™ chiral column.

Synthesis of (*R*)-(+)-2-phenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile (9). To a solution of (*S*)-**3** alcohol (44 mg, 0.23 mmol) in anhydrous methylene chloride (3 mL) were added triethylamine (61 μL, 0.44 mmol) and methanesulfonyl chloride (34 μL, 0.44 mmol). After the reaction mixture was stirred for 3 h at 0°C, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer separated from the reaction mixture was washed with saturated aqueous $NaHCO_3$ solution (2×10 mL), 5% aqueous HCl solution and H_2O, dried over $MgSO_4$ and concentrated to furnish 150 mg of crude mesylated **8**. Silica gel column chromatography (*n*-hexane/ethyl acetate, 4:1) provided 57.6 mg (89%) as a clear oil. R_f 0.61 (benzene/ethyl acetate, 5:1); GC/MSD retention time (min) 10.91, (*m*/*z*) 51, 65, 79, 103, 116, 129, 145, 172 (100), 185, 202, 224, 238, 251, 281 (M^+); IR (neat) 3124, 2958, 2244, 1462, 1364, 1176, 956 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.3 Hz, 3H), 1.20–1.55 (m, 4H), 1.87–2.17 (m, 2H), 2.91 (s, 3H), 4.43 (s, 2H), 7.24–7.47 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.8, 27.1, 35.9, 38.1, 48.7, 73.2, 120.3, 126.7, 129.2, 129.7, 134.6; Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.70; H, 6.86; N, 4.87.

To a solution of mesylated **8** (57 mg, 0.20 mmol) in DMSO (3 mL) was added 1,2,4-triazole sodium derivative (91 mg, 1 mmol). The mixture was heated at 105°C for 10 h, then cooled to room temperature and partitioned between methylene chloride and water. The organic layer was concentrated to furnish crude triazole derivative **9** (60 mg). Purification by silica gel column chromatography (*n*-hexane/ethyl acetate, 2:1) provided 46 mg (90%) as a clear oil. R_f 0.28 (*n*-hexane/ethyl acetate, 1:1); $[\alpha]_D^{31}=+60.9$ (*c* 0.55, methanol); GC/MSD retention time 10.71 min, (*m*/*z*) 55, 63, 82, 91, 103, 116, 145 (100), 172, 185, 195, 211, 225, 239, 254 (M^+); IR (neat) 3122, 2956, 2872, 2240, 1508, 1450, 1350, 1274, 1208, 1138 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (t, *J*=7.2 Hz, 3H), 1.28–1.53 (m, 4H), 1.84–2.23 (m, 2H), 4.50 (d, *J*=14.2 Hz, 1H), 4.66 (d, *J*=14.2 Hz, 1H), 7.28–7.42 (m, 5H), 7.77 (s, 1H), 7.89 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 23.1, 27.5, 35.7, 51.6, 58.2, 122.2, 126.7, 128.5, 129.4, 136.4, 144.6, 152.2; Anal. Calcd for $C_{15}H_{18}N_4$: C, 70.84; H, 7.13; N, 22.03. Found: C, 70.55; H, 7.23; N, 21.50.

Synthesis of (*S*)-(−)-2-phenyl-2-(1*H*-1,2,4-triazol-1-ylmethyl)hexanenitrile (11). Under the same procedures as above, enantiopure triazole derivative (*S*)-**11** was obtained in 92% yield. $[\alpha]_D^{31}=-61.4$ (*c* 0.55, methanol).

Synthesis of (±)-2-cyano-2-phenylhexanoic acid (4). To a solution of (±)-**3** (0.8 g, 3.94 mmol) in acetone (10 mL) was added Jones reagent (1N aqueous H_2SO_4 solution, 6 mL) at 0°C. After stirring for 3 h at room temperature, the reaction mixture was quenched with cold ice water (20 mL) and extracted with diethyl ether (2×20 mL). The combined organic extracts was washed with water, dried over $MgSO_4$ and concentrated to furnish 710 mg of crude (±)-acid **4** as a viscous oil. This acid was used without further purification in the next step. R_f 0.45 (ethyl acetate/methanol, 1:1); GC/MSD retention time (min) 4.15, (*m*/*z*) 57, 63, 77, 89, 103, 117 (100), 130, 144, 156, 173 (M^+-44); IR (neat) 3480, 3122, 2962, 2870, 2254, 1716, 1452, 1380, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.86 (t, *J*=6.8 Hz, 3H), 1.20–1.41 (m, 4H), 2.01–2.10 (m, 1H), 2.17–2.23 (m, 1H), 7.30–7.37 (m, 3H), 7.50–7.55 (m, 2H), 10.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.7, 27.8, 37.8, 55.5, 119.3, 126.5, 129.1, 129.4, 134.7, 173.2; Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 69.60; H, 6.97; N, 6.03.

Synthesis of *N*-[(*R*)-α-methylbenzyl]-2-cyano-2-phenylhexanamide (5). To a stirred solution of crude (±)-acid **4** (300 mg, 1.38 mmol) in anhydrous methylene chloride (3 mL) and dimethylformamide (3 mL) was added 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one (270 mg, 1.66 mmol) and DCC (341 mg, 1.66 mmol) at 0°C. After the mixture was stirred for 30 min, (*R*)-(+)-α-methylbenzylamine (201 mg, 1.66 mmol) was added at 0°C. After the mixture

was stirred for 3 h at room temperature, ethyl acetate (20 mL) was added. After removing the white solid by filtering, the filtrate was washed with saturated aqueous $NaHCO_3$ solution, brine, dried over $MgSO_4$ and concentrated to furnish 600 mg of crude **5** as diastereomeric mixtures. Silica gel column chromatography (*n*-hexane/ethyl acetate, 10:1) provided 380 mg (86%) of diastereomeric amide as a white solid. The recrystallization of compound **5** from methanol gave *N*-[(*R*)-α-methylbenzyl]-(2*S*)-cyano-2-phenylhexanamide **6** (70 mg); mp 100–103°C; R_f 0.49 (*n*-hexane/ethyl acetate, 2:1); $[\alpha]_D^{20}=+25.1$ (*c* 0.15, methanol); GC/MSD retention time (min) 12.22, (*m*/*z*) 51, 77, 91, 105 (100), 130, 145, 173, 190, 201, 215, 248, 277, 305, 320 (M^+); IR (KBr) 3370, 3150, 2964, 2932, 2868, 2238, 1686, 1652, 1526, 1450, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (t, J=3.6 Hz, 3H), 1.25 (m, 4H), 1.37 (d, J=11.1 Hz, 3H), 2.06 (m, 1H), 2.38 (m, 1H), 5.04 (m, 1H), 6.38 (d, J=7.4 Hz, 1H), 7.26–7.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 21.9, 22.1, 28.0, 38.3, 50.5, 54.8, 120.7, 126.3, 126.4, 128.0, 129.1, 129.2, 129.5, 135.9, 142.7, 165.9; Anal. Calcd for $C_{21}H_{24}N_2O$: C, 78.71; H, 7.55; N, 8.74. Found: C, 78.90; H, 7.61; N, 8.78.

***N*-[(*R*)-α-methylbenzyl]-(2*R*)-cyano-2-phenylhexanamide 7.** Mp 71–74°C; R_f 0.52 (*n*-hexane/ethyl acetate, 2:1); $[\alpha]_D^{20}=-17.7$ (*c* 0.15, methanol); GC/MSD retention time (min) 12.08, (*m*/*z*) 51, 77, 91, 105 (100), 130, 145, 173, 190, 201, 215, 249, 264, 277, 305, 320 (M^+); IR (KBr) 3312, 3122, 2964, 2932, 2870, 2240, 1684, 1652, 1528, 1450, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, J=3.6 Hz, 3H), 1.25 (m, 4H), 1.37 (d, J=11.1 Hz, 3H), 2.06 (m, 1H), 2.38 (m, 1H), 5.04 (m, 1H), 6.35 (d, J=7.3 Hz, 1H), 7.26–7.60 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 22.1, 22.7, 28.0, 37.9, 50.4, 54.8, 120.7, 126.1, 126.4, 127.8, 129.0, 129.2, 129.5, 135.8, 142.5, 165.7.

X-Ray crystallographic analysis

The X-ray crystallographic data were collected at 293 K on an Enraf-Nonius CAD4 automated diffractometer equipped with a Mo X-ray tube and a graphite crystal monochromator; crystal data for (1*R*,2*S*)-**6**: $C_{21}H_{24}N_2O$, M=320.42, monoclinic, C2 (#5), a=20.003 (4), b=8.612 (4), c=11.063 (2) Å, α=90, β=99.97 (2), γ=90, V=876.9 (9) $Å^3$, Z=4, D_c=1.134 g cm^{-3}, F(000)=688. Final R indices: R_1=0.0588, wR_2=0.1440.

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