One-Pot Synthesis of Optically Active Cyanohydrin Acetates from Aldehydes via Quinidine-Catalyzed Transhydrocyanation Coupled with Lipase-Catalyzed Kinetic Resolution in Organic Solvent

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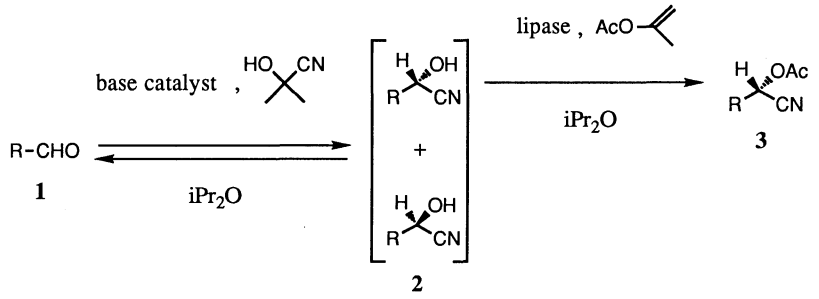
A novel one-pot synthetic method was developed for the preparation of optically active cyanohydrin acetates. Racemic cyanohydrins were generated from aldehydes and acetone cyanohydrin by quinidine-catalyzed transhydrocyanation, and the resulting cyanohydrins **2a**—**j** were then acetylated by lipase in a stereoselective manner using isopropenyl acetate as an acylating regent. A variety of aldehydes **1a**—**j** were successfully transformed into the corresponding cyanohydrin acetates **3a**—**j** having 47—95% e.e. without isolating the unstable cyanohydrins **2**. Moreover, the reversible nature of base-catalyzed transhydrocyanation allows for in situ racemization of the unreacted cyanohydrins and concurrent kinetic resolution by lipase enabled the preparation of (*S*)-**3b**—**d** with 40—82% e.e. in more than 50% yield. Polymer-supported cinchona alkaloid was also used as a catalyst for this one-pot reaction and showed the comparable chemical and optical yield to that for the soluble monomeric alkaloid. The insoluble polymer and lipase were recovered by filtration and found to have almost the same catalytic activity even after four times of reuse.

Cyanohydrins are important starting materials for the synthesis of pharmaceuticals and pesticides because cyanohydrins are easily converted into multifunctional chiral building blocks such as β-amino alcohols,[1] α-hydroxy carboxylic acids,[2] and α-hydroxy ketones.[3] So far chemical[4,5] and biochemical[1-3,6] approaches for the preparation of optically active cyanohydrins have been reported. However, cyanohydrins are relatively unstable and susceptible to decomposition or racemization particularly in aqueous solution. The use of organic solvent is one of the solution to this drawback since cyanohydrins are more stable in organic solvent than in aqueous buffer. Several approaches using organic solvent in this regard have been reported for the preparation of optically active cyanohydrins by enzymatic addition of hydrogen cyanide to the aldehydes[7] or lipase-catalyzed kinetic resolution of racemic cyanohydrins.[8] Even in organic solvent, however, cyanohydrins undergo decomposition or racemization to some extent and the yield of cyanohydrin was often lowered.[8a] The reversible nature of the interconversion of cyanohydrins to aldehydes forced us to combine in situ generation of unstable cyanohydrins from aldehydes with lipase-catalyzed kinetic resolution in organic solvent. We now report a novel one-pot synthesis of optically active cyanohydrin acetates **3** by quinidine-catalyzed in situ generation of cyanohydrins **2** from aldehydes **1** and acetone cyanohydrin, coupled with lipase-catalyzed stereoselective acetylation of cyanohydrins **2** in organic solvent (Scheme 1).

In this reaction, the labile cyanohydrins **2** are generated and served on the spot for kinetic resolution without isolation. The acetylation of the hydroxyl group in cyanohydrins should prevent the initial step of the elimination of hydrogen cyanide from cyanohydrins;[9] consequently, the decomposition or racemization of cyanohydrins should be greatly reduced and the cyanohydrin acetates **3** becomes stereochemically stable.



Scheme 1.

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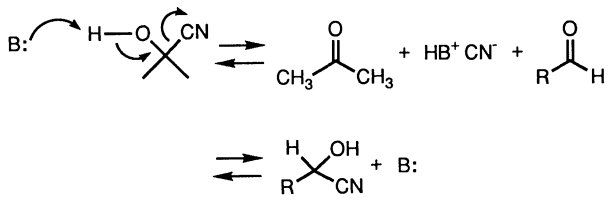
As a source of hydrogen cyanide, acetone cyanohydrin was chosen because this is less toxic and easier to handle than hydrogen cyanide gas. Acetone cyanohydrin releases hydrogen cyanide in the presence of a base catalyst and reacts with aldehydes to give cyanohydrins;[5] acetone is the sole by-product in this reaction and has no adverse effect on lipase activity. Importantly, acetone cyanohydrin is a tertiary alcohol and is not accepted as a substrate by lipase due to its steric bulkiness, hence remaining as an active HCN donor during the reaction.#

Results and Discussion

One-Pot Synthesis of Optically Active Cyanohydrin Acetates from Aldehydes. Base-catalyzed cyanohydrin formation is considered to proceed as follows: the elimination of hydrogen cyanide from acetone cyanohydrin is initiated by the abstraction of a hydroxyl proton with a base and the reverse addition of the intermediary cyanide-base complex to the carbonyl group of the other aldehyde gives the second cyanohydrin.



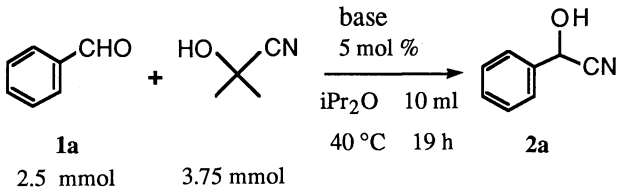
Ogata et al. reported that the addition of HCN to aldehydes was slow in aprotic nonpolar solvents, and the rate constant increased with increasing the dielectric constant of the solvent.[9] In the present study, however, diisopropyl ether was the solvent chosen because of the high activity of lipase in nonpolar aprotic solvent.[10] Therefore an effective base catalyst was required to accelerate the cyanohydrin formation in diisopropyl ether. Cinchona alkaloid is a promising candidate for such an effective base catalyst because it is a bifunctional catalyst and a tertiary amine moiety in the quinuclidine ring works as a base and the hydroxyl group placed next to the amine moiety serves as an acid.[11] Accordingly, cinchona alkaloids such as quinidine (**4a**) and its diastereoisomer, quinine (**4b**) should accelerate the transhydrocyanation much more effectively than simple tertiary amines because the hydroxyl group in the catalyst is expected to assist the elimination of hydrogen cyanide by giving a proton to the cyanide ion to be eliminated. In fact, cinchona alkaloid was used as a catalyst for the stereoselective addition of HCN to benzaldehyde.[12]

#Acetone cyanohydrin (5.0 mmol) was not acetylated at all by the lipase from *Pseudomonas* sp. M-12-33 (Amano, 250 mg) after 8.7 d incubation at 40 °C in the presence of isopropenyl acetate (7.5 mmol) as an acylating reagent in dry diisopropyl ether (20 mL).

Six organic bases including cinchona alkaloid were tested for their catalytic activity for the formation of mandelonitrile (**2a**) from benzaldehyde (**1a**) and acetone cyanohydrin. Benzaldehyde was allowed to react with 1.5 equivalents of acetone cyanohydrin in diisopropyl ether in the presence of 5 mol% of the base catalysts (Scheme 2).

Among the bases tested (Table 1), quinidine (**4a**) and quinine (**4b**) were the most efficient catalysts as expected, affording mandelonitrile (**2a**) in 85 and 83% yield in 19 h. Under the same reaction conditions, brucine (**5**) and triethylamine gave only 58 and 20% of mandelonitrile, respectively. 2-(Dimethylamino)ethanol (**6**) and 1-(diethylamino)-2-propanol (**7**) both having β-hydroxyamino function like cinchona alkaloid were found much less effective than quinidine and quinine and no reaction was observed without catalyst or with the lipase from *Pseudomonas* sp. M-12-33 (Amano).

Since quinidine (**4a**) and quinine (**4b**) are chiral bases, the addition of hydrogen cyanide was anticipated at first to be stereoselective and hence the optically active mandelonitrile (**2a**) would be obtained. Contrary to our initial expectation, however, the mandelonitrile formed under the catalysis by **4a** and **4b** was racemic. The addition of HCN to aldehyde is reversible, which probably rendered the addition of hydrogen cyanide thermodynamically controlled and resulted in the racemization of the product mandelonitrile. Since an



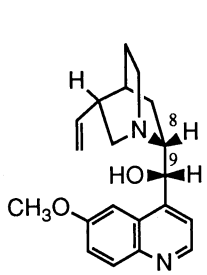
1a 2.5 mmol 3.75 mmol **2a**

Scheme 2.

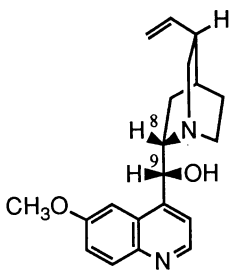
Table 1. Catalytic Activity of Organic Bases for Transhydrocyanation between Benzaldehyde (**1a**) and Acetone Cyanohydrin[a]

Base catalyst	Yield of **2a**[b] / %
Quinidine (**4a**)	85[c]
Quinine (**4b**)	83[c]
Brucine (**5**)	20[c]
NEt_3	58
$Me_2NCH_2CH_2OH$ (**6**)	34
$Et_2NCH_2CH(CH_3)OH$ (**7**)	25
Lipase[d]	0
None	0

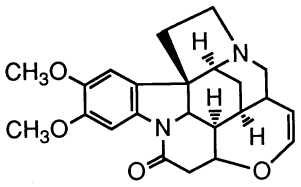
a) Conditions: benzaldehyde (**1a**) (2.5 mmol), acetone cyanohydrin (3.75 mmol), base catalyst (0.125 mmol), *i*-Pr_2O (10 mL), 40 °C, 19 h. b) Determined by ^1H NMR. c) Cyanohydrin **2a** was converted into the acetate **3a** (Ac_2O, pyridine) and found to be racemic (^1H NMR, $Eu(hfc)_3$). d) The commercial lipase from *Pseudomonas* sp. M-12-33 (Amano)(25 mg) was added.



(8*R*,9*S*)-quinidine (**4a**)



(8*S*,9*R*)-quinine (**4b**)

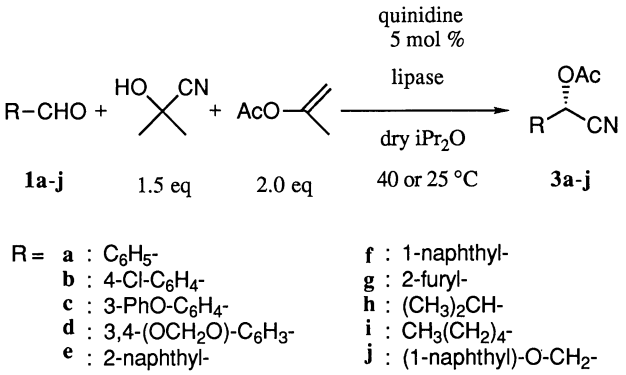


brucine (**5**)

effective conversion of aldehydes into racemic cyanohydrins was thus achieved under the catalysis of cinchona alkaloid in diisopropyl ether, this process was coupled with enzymatic acetylation of cyanohydrins.

We previously reported that the lipases from *Pseudomonas* species (Amano and Toyobo Co.) were effective for stereoselective acetylation of racemic mandelonitrile in diisopropyl ether,[8a] and these lipases were used for the reaction of aldehydes **1a**—**j** (Scheme 3).

Aldehyde **1** was allowed to react with acetone cyanohydrin (1.5 equiv) and isopropenyl acetate (2.0 equiv) in the presence of quinidine (**4a**) (5 mol%) and the lipase in diisopropyl ether at 40 °C. The progress of the reaction was checked by ^{1}H NMR with monitoring the signals of the substrate aldehydes **1** (CHO), the



Scheme 3.

cyanohydrins **2** [CH(CN)], and the acetates **3** [CH(CN)]. When a proper conversion was attained (21—45%), the reaction mixture was filtered and the concentrated filtrate was chromatographed on silica gel to isolate the acetates **3**. The results were summarized in Table 2.

Benzaldehyde (**1a**) was transformed into (*S*)-mandelonitrile acetate (**3a**) with 83% e.e. by the lipase from *Pseudomonas* sp. M-12-33 (Amano) in 34% isolated yield based on the aldehyde **1a**. (*R*)-Mandelonitrile (**2a**) was also separated from the reaction mixture (Entry 1), but found to be contaminated with benzaldehyde (**1a**) even after the purification by column chromatography, suggesting that **2a** was decomposed on silica gel during the chromatographic separation. Thus crude **2a** was purified as *t*-butyldimethylsilyl ether, and the acid deprotection of silyl group gave pure (*R*)-**2a** with only 21% e.e. in 22% overall yield from aldehyde. The low e.e. value of (*R*)-**2a** indicated that **2a** was partially racemized by the quinidine-catalyzed reversible transhydrocyanation. Hence, only acetates **3b**—**j** were isolated in Entry 2—10.

Table 2. One-Pot Synthesis of Optically Active Cyanohydrin Acetates **3a**—**j** from Aldehydes **1a**—**j**[a]

Entry	Aldehyde	Lipase prep.[b] abb.	React. time d	Ratio[c] **1** : **2** : **3** %			Isolated yield of **3**[d] %	e.e. of **3**[e] %	Absolute config.[f]
1	**1a**	A	1.6	21	42	37	34	83	*S*
2	**1b**	A	5.9	16	39	45	39	81	*S*
3	**1c**	A	2.5	28	34	38	20	83	*S*
4	**1d**	A	4.1	45	30	25	22	95	*S*
5	**1e**	B	1.8	40	27	34	30	91	*S*
6	**1f**	B	1.8	26	53	25	20	93	*S*
7	**1g**	A	2.0	35	20	45	42	47	*R*
8[g]	**1h**	A	3.0	0	79	21	15	69	*S*
9[g]	**1i**	B	3.4	0	67	33	27	75	*S*
10	**1j**	A	2.8	0	56	44	28	74	*R*

a) Typical conditions: aldehyde **1a** (40 mmol), acetone cyanohydrin (60 mmol), isopropenyl acetate (80 mmol), *i*-Pr_2O (160 mL), quinidine (**4a**) (2 mmol), lipase (2.0 g), 40 °C. b) Lipases used were: A, commercial lipase from *Pseudomonas* sp. M-12-33 (Amano Pharm. Co., Ltd). B, lipase from *Pseudomonas* sp. (Toyobo Co., Ltd.) immobilized onto Hyflo Super-Cel. c) Determined by ^{1}H NMR of the reaction mixture. d) Isolated yield based on **1**. e) Determined by ^{1}H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$. f) The configurations of **3a**, **3c**, **3d**, **3i**, and **3j** were determined by comparing the optical rotation values with the reported ones. The absolute configurations of **3b**, **3e**, **3f**, **3g**, and **3h** were determined by comparing the optical rotation values with those of the authentic samples. Preparation of the authentic samples are described in Experimental section. g) Reaction temperature was 25 °C.

All the reactions were clean: No side reaction such as benzoin condensation was observed at all. The formation of the acetate **3a** was not detected after a prolonged incubation of mandelonitrile (**2a**) and isopropenyl acetate in the presence of quinidine (**4a**).

The substituted benzaldehydes **1b—d** were also converted into the corresponding (*S*)-acetates **3b—d** with up to 95% e.e. in 20—39% yield by the lipase from *Pseudomonas* sp. M-12-33 (Amano). The *S* isomer of **3c** is the desired enantiomer for the preparation of pyrethroids of high insecticidal activity.[13] Also (*S*)-**3d** can be transformed into the active enantiomer of noradrenaline.[6f] The lipase from *Pseudomonas* sp. (Toyobo) showed high stereoselectivity for the naphthaldehydes **1e,f**, affording (*S*)-**3e,f** with 91 and 93% e.e., respectively. 2-Furaldehyde (**1g**) and aliphatic aldehydes **1h—j** were also accepted as a substrate by the lipases and converted into the corresponding acetates **3h—j** with 47—75% e.e.

The e.e. of the acetates **3a—j** were determined by ^{1}H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$; the base-line separated peaks of acetyl proton enabled the calculation of the e.e. precisely. The absolute configurations of **3a**, **c**, **d**, **i**, and **j** were determined by comparing the observed optical rotation with reported ones.[4e,6a,d,f,14] Since the optical rotation values were not reported for **3b**, **e—h**, their configurations were correlated with those of the corresponding cyanohydrins **2b**, **e—h** whose absolute configuration and optical rotation were reported (see Experimental). The preferentially acetylated stereoisomer by lipase was also found to have the same configuration for these compounds.

Lipase-Catalyzed Kinetic Resolution of Cyanohydrins with in situ Racemization. As described above, the unchanged cyanohydrin **2a** was partially racemized by quinidine-catalyzed reversible transhydrocyanation and the cyanohydrin generated by quinidine was racemic. If a pre-equilibrium between cyanohydrins **2** and aldehydes **1** exists and the racemization is faster than the lipase-catalyzed acetylation, the kinetic resolution of racemic cyanohydrins would then proceed with in situ racemization of the substrate cyanohydrin. This type of enzymatic second-order asymmetric transformation has been attained so far in aqueous medium by the abstraction of an acidic proton from an asymmetric center.[15] In organic solvent, on the other hand, such proton abstraction is slower than in aqueous medium and the e.e. of the product was decreased when the conversion exceeded 50%.[16] Accordingly it is worth investigation whether the quinidine-catalyzed reversible transhydrocyanation offers another promising method for racemization operative even in nonpolar and aprotic solvent. Thus, the reactions of **1b—e** (Scheme 3) were kept going until the conversion of the reactions exceeded 50% (Table 3). The best result was obtained for the reaction of the aldehyde **1d** catalyzed by the lipase from *Pseudomonas* sp. M-12-33 (Amano) (Entry 3): The acetate **3d** with 82% e.e. was obtained in 69% isolated yield from the aldehyde **1d** after 13.7 d. Since 20% of aldehyde **1d** was found to remain in the reaction mixture by a ^{1}H NMR analysis, the conversion yield of the cyanohydrin **2d** from the aldehyde **1d** was calculated as 80% and the conversion yield of the acetylation (**2d→3d**) was found to be 91%. As in a nature of kinetic resolution, the e.e. of the product decreases with the conversion of the reaction;[17] however, the e.e. of **3d** still remained in high value (82% e.e.) in spite of high conversion (91%) of the enzymatic process. In the far right column in Table 3, were shown the e.e. values which were calculated on an assumption that in situ racemization did not occur and that the lipase had a perfect stereoselectivity in a sense that no (*R*)-isomer was acetylated before the complete consumption of (*S*)-isomer. These values, for example, indicate that the maximum e.e. of (*S*)-**3d** cannot exceed 10% if **2d** had not undergone in situ racemization. The reactions in which the conversion of the acetylation (**2b,c,e→3b,c,e**) reached 78—97% (Entry 1,2 and 4) gave (*S*)-**3b,c,e** with 40—62% e.e. These values are evidently higher than the calculated e.e.'s for simple kinetic resolution without in situ racemization. These results are best explained in

Table 3. Lipase-Catalyzed Kinetic Resolution of Cyanohydrins **2** Generated from Aldehydes **1** with in situ Racemization by Quinidine-Catalyzed Reversible Transhydrocyanation[a]

Entry	Aldehyde	Lipase prep.[b] abb.	React. time	Conversion[c] **1→2**	Conversion[c] **2→3**	Isolated yield of **3**[d]	E.e. of (*S*)-**3**[e]	Calcd max. e.e. of (*S*)-**3**[f]
			d	%	%	%	%	(%)
1	**1b**	A	16.6	92	78	40	61	(28)
2	**1c**	A	13.7	81	88	68	62	(14)
3	**1d**	A	16.7	80	91	69	82	(10)
4	**1e**	B	4.4	94	97	89	40	(3)

a) Typical conditions: aldehyde **1b** (1 mmol), acetone cyanohydrin (1.5 mmol), isopropenyl acetate (2.0 mmol), quinidine (**4a**) (0.05 mmol), lipase (100 mg), *i*-Pr$_2$O (8 mL), 40 °C. b) Lipases used were: A, Commercial lipase from *Pseudomonas* sp. M-12-33 (Amano); B, lipase from *Pseudomonas* sp. (Toyobo) immobilized onto Hyflo Super-Cel. c) Determined by ^{1}H NMR. d) Isolated yield of **3** from **1**. e) Determined by ^{1}H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$. f) Calculated maximum e.e. of (*S*)-**3** with the assumption that in situ racemization did not occur.

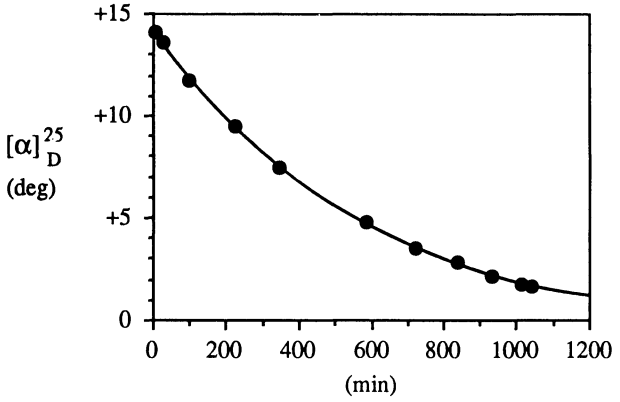


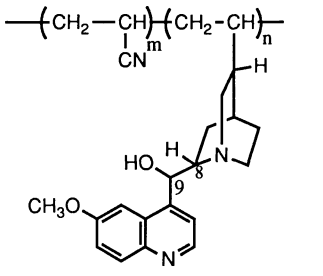
Fig. 1. Time course of the racemization of optically active cyanohydrin **2c** catalyzed by quinidine (10 mol% equiv) in diisopropyl ether. Conditions: (*R*)-**2c** (87% e.e., 34.0 mg, 0.151 mmol), acetone cyanohydrin (106.4 mg, 1.25 mmol), quinidine (4.9 mg, 0.015 mmol) in dry diisopropyl ether (1 ml), 25 °C.

terms of in situ racemization of the unchanged enantiomer of cyanohydrin **2** coupled with successive kinetic resolution by lipase to convert into (*S*)-acetate **3**. In order to certificate this, racemization of (*R*)-**3c** was performed in the presence of quinidine in diisopropyl ether (Fig. 1). The half-life ($t_{1/2}$) of the optical activity of (*R*)-**2c** was 346 min at 25 °C, and thus racemization was indeed faster than enzymatic acetylation. Accordingly, quinidine-catalyzed transhydrocyanation is a novel method for racemization operative even in diisopropyl ether instead of the abstraction of an acidic proton from an asymmetric center, and thus an effective second-order asymmetric transformation was accomplished for the first time by lipase in organic solvent.

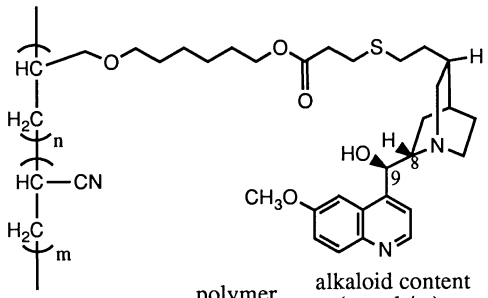
Application of Polymer-Supported Quinidine and Quinine as a Catalyst for One-Pot Synthesis of Optically Active Cyanohydrin Acetates. One of the convenient methods to improve the efficiency of a catalyst is to immobilize it onto insoluble polymer matrix. Several polymer-supported cinchona alkaloids have been prepared so far and used for various asymmetric reactions such as Michael addition,[18a-c,e] conjugated addition of thiol,[18c,e] epoxidation,[18d] and ring opening of acid anhydrides.[18e] Recently, the polymeric cinchona alkaloid was used as a catalyst for the asymmetric addition of HCN to 3-phenoxybenzaldehyde.[19] If the polymer-supported cinchona alkaloid is applied to the present reaction, both the insoluble polymer and the lipase could be recovered and reused.

According to the reported procedure,[18d,20] the polymeric quinidine **8a**, quinine **8b**, and the polymer **9** holding quinine via 15 atom-length of spacer were prepared and used as a base catalyst for the one-pot synthesis of cyanohydrin acetates **3b**—**d** with in situ racemization (Scheme 3).

The alkaloid content in the polymers **8a**, **b**, and **9** was



polymer	alkaloid content (mmol/g)
(8*R*,9*S*)-**8a**	0.42
(8*S*,9*R*)-**8b**	0.34



polymer	alkaloid content (mmol / g)
(8*S*,9*R*)-**9**	0.21

determined by elemental analysis, and the polymers were added so that the amount of alkaloid moiety in the polymers became 5 mol% to the aldehydes **1**.

These polymer-catalysts were insoluble in diisopropyl ether, and the reaction proceeded in heterogeneous suspension for both lipase and the polymer. The results are summarized in Table 4. When the polymer **8a** was used (Entry 1), (*S*)-**3b** with 81% e.e. was obtained at 85% conversion of the acetylation (**2b**→**3b**). Acetate (*S*)-**3c** with 74% e.e. was afforded at 86% conversion (**2c**→**3c**) when the polymer **9** was used (Entry 6). The polymer **8b** gave (*S*)-**3d** with 92% e.e. (Entry 8) when the conversion of acetylation (**2d**→**3d**) reached 79%. Although the polymer **9** has a spacer of 15 atom-length between the quinine portion and the polymer chain, the conversion and e.e. of (*S*)-acetate **3b**—**d** were almost comparable to those when the polymers **8a** and **b** were used.

Optical yields of the reactions with the polymer catalysts **8** and **9** were almost equal to or somewhat higher than those catalyzed by monomer quinidine (**4a**) (Table 3, Entry 1—3), and no remarkable difference was observed in terms of their catalytic activity. However, the major advantage of the polymers **8** and **9** is that the polymers can be recovered and reused: The polymer **8b** and **9** were recovered together with the lipase powder, and the mixture was dried in a desiccator (P_2O_5, more than 3 days) and reused for the reaction of aldehyde **1c** (Table 5). The polymers **8b** and **9** had almost the same catalytic activity after three or four times of reuse.

In summary, a new system for kinetic resolution of

Table 4. Application of Polymer-Supported Cinchona Alkaloid **8a**, **b**, and **9** for Lipase-Catalyzed Kinetic Resolution of Cyanohydrins **2** Generated from Aldehydes **1** with in situ Racemization by Reversible Transhydrocyanation[a]

Entry	Aldehyde	Polymer catalyst[b]	React. time	Conversion[c]		Isolated yield of **3**[d]	e.e. of (*S*)-**3**[e]	Calcd max. e.e. of (*S*)-**3**[f]
				1→**2**	**2**→**3**			
			d	%	%	%	%	(%)
1	**1b**	**8a**	13.7	91	85	54	81	(18)
2	**1b**	**8b**	8.6	84	74	45	87	(35)
3	**1b**	**9**	19.4	83	72	40	74	(38)
4	**1c**	**8a**	11.5	86	86	61	69	(16)
5	**1c**	**8b**	8.6	87	83	63	64	(21)
6	**1c**	**9**	13.0	87	86	50	74	(16)
7	**1d**	**8a**	13.7	62	85	51	86	(17)
8	**1d**	**8b**	11.5	63	79	34	92	(26)
9	**1d**	**9**	15.8	61	85	41	88	(17)

a) Conditions: aldehydes **1b**—**d** (1.0 mmol), acetone cyanohydrin (1.5 mmol), isopropenyl acetate (2.0 mmol), polymer **8a**, **b**, and **9** (0.05 mmol equiv), lipase (100 mg), *i*-Pr_2O (8 mL), 40°C. b) Alkaloid content and the amount of polymer were: **8a**, 0.44 mmol g^{-1}, 120 mg; **8b**, 0.34 mmol g^{-1}, 147 mg; **9**, 0.21 mmol g^{-1}, 240 mg. c) Determined by ^1H NMR. d) Isolated yield based on **1**. e) Determined by ^1H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$. f) Calculated maximum e.e. of (*S*)-**3** with the assumption that in situ racemization did not occur.

Table 5. Reuse of Polymer **8b** and **9** and the Lipase for One-Pot Synthesis of (*S*)-**3c** with in situ Racemization of Cyanohydrins **2c**[a]

Polymer catalyst	Number of reuse	Reaction time (days)	Conversion yield of **3c**[b] (%)	Isolated yield of **3c**[c] (%)	E.e. of (*S*)-**3c**[d] (%)
8b	1	2.0	38	35	85
8b	2	2.0	29	16	94
8b	3	2.0	28	19	90
9	1	2.0	42	23	88
9	2	2.1	44	43	85
9	3	2.0	62	52	87
9	4	2.0	42	38	85

a) Polymer **8b** (294 mg, 0.1 mmol equiv) or **9** (480 mg, 0.1 mmol equiv) and a lipase from *Pseudomonas* sp. M-12-33 (150 mg) were used for the first run. Every 2.0 days, the polymer and lipase were recovered together by filtration and dried in a desiccator over P_2O_5 (>2 days), and then reused. Conditions: 3-Phenoxybenzaldehyde (**1c**) (397 mg, 2 mmol), acetone cyanohydrin (222 mg, 2.6 mmol), isopropenyl acetate (330 mg, 3.3 mmol), the recovered polymer and lipase, dry *i*-Pr_2O (8 mL) 40°C 2.0 days. b) Determined by ^1H NMR. c) Isolated yield based on **1c**. d) Determined by ^1H NMR in the presence of a chiral shift reagent, Eu(hfc)$_3$.

racemic cyanohydrins generated in situ from aldehydes has been established. Racemic cyanohydrins were generated from various aldehydes and acetone cyanohydrin by quinidine-catalyzed transhydrocyanation, and then acetylated by lipase in a stereoselective manner using isopropenyl acetate as an acylating reagent. Aromatic and aliphatic aldehydes were successfully converted into the corresponding optically active cyanohydrin acetates without isolation of labile intermediate cyanohydrins. Moreover, due to the reversible nature of the quinidine-catalyzed transhydrocyanation between the aldehydes and cyanohydrins, the unchanged (*R*)-enantiomer was racemized while the (*S*)-enantiomer of the cyanohydrin was selectively transformed into the corresponding acetates, yielding the optically active cyanohydrin acetates **3a**—**d** with high optical yields in more than 50% of chemical yields from the corresponding aldehydes. By supporting quinidine and quinine on insoluble polymer matrix, the recycle use of the base catalysts and the lipases was attained. This new system serves as a convenient and versatile route for the preparation of optically active cyanohydrin acetates from the corresponding aldehydes.

Experimental

General. ^1H and ^{13}C NMR spectra were measured on a Varian VXR-200 spectrometer (200 MHz for ^1H). Solvent was $CDCl_3$ with TMS as an internal standard. Mass spectra were obtained on a JEOL JMX-DX-300 spectrometer. Infrared spectra were recorded on a Hitachi 215 spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed on a Yanaco MT-3. Melting points are uncorrected. The products were isolated by flash column chromatography on silica gel [Silica gel 60 (Merck No. 9385), 230—400 mesh, Merck Co.] or bulb-to-bulb distillation on a Büchi Kugelrohr distillation apparatus. Diisopropyl ether was distilled over CaH_2 and stored over molecular sieves 4 Å. The aldehydes **1a**—**i** were commercially available and purified before use by distillation or recrystallization under an argon atmosphere. The aldehyde **1j** was prepared according to the reported procedure,[6a] and its

purity was ascertained by ^{1}H NMR. Commercial grade of isopropenyl acetate was distilled before use. Quinidine was purchased from Aldrich Co. and used as such. The commercial lipase preparation from *Pseudomonas* sp. M-12-33 (Amano Pharm. Co., Ltd.) was used as such. The lyophilized powder of the lipase from *Pseudomonas* sp. (Toyobo Co., Ltd.) was immobilized by adsorption onto Hyflo Super-Cel (10 mg lipase/g Hyflo Super-Cel), according to the reported procedure.[21]

One-Pot Synthesis of Optically Active Cyanohydrin Acetates from Aldehydes. (*S*)-(+)-1-Cyano-1-phenylmethyl Acetate (3a); Typical Procedure. Benzaldehyde (**1a**) (4.24 g, 40 mmol), isopropenyl acetate (8.01 g, 80 mmol), acetone cyanohydrin (5.11 g, 60 mmol) and quinidine (649 mg, 2 mmol) were dissolved in dry diisopropyl ether (160 mL). Lipase from *Pseudomonas* sp. M-12-33 (Amano) (2.00 g) was added to the solution, and the suspension was stirred for 39 h at 40 °C under an argon atmosphere. The lipase powder was filtered off and the filtrate was concentrated in vacuo. A portion of the residual oil was analyzed by ^{1}H NMR. Three singlets [CHO proton for the aldehyde **1a** (δ=10.00), CH proton for the cyanohydrin **2a** (δ=5.55), and CH proton for the acetate **3a** (δ=6.40)] were clearly separated; the composition of the oil was calculated to be **1a** (21%), **2a** (42%), and **3a** (37%). The acetate **3a** was isolated from the mixture by flash column chromatography [hexane (5):AcOEt(1)] as a colorless oil: (2.36 g, 34%); $[\alpha]_D^{25}$=+19.3 ° (*c* 2.230, benzene), [lit,[6f] $[\alpha]_D$=−15 ° (*c* 1.9, benzene) for *R* isomer with 60% e.e.]. Optical purity of (+)-**3a** was determined as 83% by ^{1}H NMR in the presence of a chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) drivative, Eu(hfc)$_3$ [ca. 10 mg for 5 mg of **3a** in 800 μl of $CDCl_3$; δ(OAc)=3.01 (*R*) and 3.14 (*S*)]. IR (neat) 2250 (C≡N) and 1755 (C=O) cm^{-1}; ^{1}H NMR δ=2.17 (3H, s, OAc), 6.41 (1H, s, CH), and 7.42—7.56 (5H, m); ^{13}C NMR δ=20.47 (*C*H$_3$CO), 62.85 (CH), 116.11 (C≡N), 127.88, 129.25, 130.41, 131.74, and 168.93 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 175 (M$^+$, 6), 133 (35), 116 (28), 115 (41), 105 (16), 89 (10), and 43 (100). Anal. Calcd for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 8.00%. Found: C, 68.34; H, 5.23; N, 7.90%. Further elution of the column afforded crude (*R*)-**2a** (2.61 g) containing benzaldehyde (**1a**) and acetone cyanohydrin. The crude **2a** was converted into *t*-butyldimethylsilyl ether by the usual manner followed by flash column chromatography [hexane (8): AcOEt (1)]: (600 mg, 23% from **1a**); $[\alpha]_D^{25}$=+3.8 ° (*c* 1.00, $CHCl_3$). ^{1}H NMR δ=0.15 and 0.23 (2×3H, 2×s, Si(CH$_3$)$_2$), 0.94 (9H, s, ^{t}Bu), 5.52 (1H, s, CH), and 7.37—7.51 (5H, m). Acid deprotection gave (*R*)-mandelonitrile (**2a**) as a colorless oil: (277.6 mg, 22% from **1a**). $[\alpha]_D^{25}$=+8.63 ° (*c* 5.552, $CHCl_3$) [lit,[22] $[\alpha]_D$=+43.5 ° (*c* 5, $CHCl_3$) for *R* isomer with 92.5% e.e.]; ^{1}H NMR δ=2.90 (1H, br s, OH), 5.55 (1H, s, CH), and 7.40—7.58 (5H, m). Acetylation of (*R*)-(+)-**2a** gave (*R*)-(−)-**3a**; 21% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.31 (*R*) and 2.33 (*S*)].

Compounds **3b**—**j** were prepared by the same procedure from the corresponding aldehydes **1b**—**j**. Only the starting aldehyde, purification method, yield, physical and spectroscopic data are given for each cyanohydrin acetate **3b**—**j**.

(*S*)-(+)-1-Cyano-1-(4-chlorophenyl)methyl Acetate (3b). Prepared from 4-chlorobenzaldehyde (**1b**). Flash column chromatography on silica gel eluting with [hexane (8):AcOEt (1)] gave a colorless oil: (818 mg, 39%); $[\alpha]_D^{25}$=+31.2 ° (*c* 2.08, benzene); 81% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.34 (*R*) and 2.36 (*S*)]; IR (neat) 2250 (C≡N) and 1755 (C=O) cm^{-1}; ^{1}H NMR δ=2.17 (3H, s, OAc), 6.38 (1H, s, CH), and 7.39—7.52 (4H, m); ^{13}C NMR δ=20.41 (*C*H$_3$CO), 62.16 (CH), 115.81 (C≡N), 129.28, 129.50, 130.29, 136.58, and 168.82 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 209 (M$^+$, 6), 211 ([M+2]$^+$, 2), 167 (21), 149 (32), 114 (14), and 43 (100); Anal. Calcd for $C_{10}H_8ClNO_2$: C, 57.30; H, 3.85; N, 6.68%. Found: C, 57.46; H, 3.88; N, 6.87%. The absolute configuration of (+)-**3b** was determined by comparing its optical rotation with that of the authentic sample (*R*)-(−)-**3b** derived from the optically active cyanohydrin (*R*)-(+)-**2b** with a known configuration (vide infra).

(*S*)-(+)-1-Cyano-1-(3-phenoxyphenyl)methyl Acetate (3c). Prepared from 3-phenoxybenzaldehyde (**1c**). Flash column chromatography on silica gel eluting with [hexane (6): AcOEt(1)] followed by rechromatography eluting with [hexane (40):AcOEt(1)] gave a colorless oil: (540 mg, 20%); $[\alpha]_D^{27}$=+21.25 ° (*c* 10.27, benzene) [lit,[14] $[\alpha]_D^{20}$=+17.1 ° (*c* 10, benzene) for *S* isomer]; 83% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.34 (*R*) and 2.36 (*S*)]; IR (neat) 2250 (C≡N) and 1760 (C=O) cm^{-1}; ^{1}H NMR δ=2.17 (3H, s, OAc), 6.36 (1H, s, CH), and 6.99—7.44 (9H, m); ^{13}C NMR δ=20.45 (*C*H$_3$CO), 62.43 (CH), 115.90 (C≡N), 117.69, 119.39, 120.09, 122.10, 124.11, 130.00, 130.64, 133.45, 156.18, 158.20, and 168.83 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 267 (M$^+$, 52), 225 (100), 206 (7), 197 (11), 181 (19), 147 (12), 114 (36), 77 (29), 51 (25), and 43 (49); Anal. Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24%. Found: C, 71.81; H, 4.92; N, 5.48%.

(*S*)-(+)-1-Cyano-1-(3,4-methylenedioxyphenyl)methyl Acetate (3d). Prepared from 3,4-(methylenedioxy)benzaldehyde (**1d**). Preparative thin-layer chromatography on silica gel developed with [hexane (5):AcOEt (1)] for 3 times yield **3d** as a colorless oil: (35.7 mg, 27%); $[\alpha]_D^{25}$=+36.9 ° (*c* 1.77, benzene) [lit,[6f] $[\alpha]_D$=−44 ° (*c* 1.7, benzene) for *R* isomer with 99.5% e.e.]; 85% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.50 (*R*) and 2.56 (*S*)]; IR (neat) 2250 (C≡N) and 1755 (C=O) cm^{-1}; ^{1}H NMR δ=2.15 (3H, s, OAc), 6.03 (2H, s, OCH$_2$O), 6.31 (1H, s, CH), 6.84 (1H, m, 6′-H), 6.99 (1H, m, 2′-H), and 7.01 (1H, m, 5′-H); ^{13}C NMR δ=20.50 (*C*H$_3$CO), 62.67 (CH), 101.79 (OCH$_2$O), 108.22, 108.64, 116.15 (C≡N), 122.44, 125.36, 148.41, 149.40, and 168.92 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 219 (M$^+$, 88), 177 (100), 160 (99), 159 (100), 149 (29), 130 (21), 129 (22), 102 (34), 75 (32), 63 (28), 51 (28), and 43 (86); Anal. Calcd for $C_{11}H_9NO_4$: C, 60.28; H, 4.14; N, 6.39%. Found: C, 59.98; H, 4.25; N, 6.53%.

(*S*)-(+)-1-Cyano-1-(2-naphthyl)methyl Acetate (3e). Prepared from 2-naphthaldehyde (**1e**). Flash column chromatography on silica gel eluting with [hexane (8):AcOEt (1)] and followed by rechromatography eluting with hexane (12):AcOEt (1) gave **3e** as a white crystalline solid: (968 mg, 43%); mp 35 °C; $[\alpha]_D^{25}$=+21.7 ° (*c* 1.01, $CHCl_3$); 85% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.66 (*R*) and 2.71 (*S*)]; IR (KBr) 2245 (C≡N) and 1755 (C=O) cm^{-1}; ^{1}H NMR δ=2.18 (3H, s, OAc), 6.58 (1H, s, CH), 7.50—7.61 (3H, m), 7.82—7.95 (3H, m), and 8.02 (1H, m); ^{13}C NMR δ=20.52 (*C*H$_3$CO), 63.07 (CH), 116.17 (C≡N), 124.28, 127.09, 127.59, 127.83, 128.02, 128.38, 128.92, 129.45, 132.85, 133.88, and 168.99 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 225 (M$^+$, 31), 183 (80), 166 (63), 165 (100), 155 (19), 139 (21), 127 (26), and 43 (72); Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.65; H, 4.93; N, 6.25%. The absolute configuration of (+)-**3e** was determined by comparing its optical rotation with that of the

authentic sample (*R*)-(−)-**3e** derived from the optically active cyanohydrin (*R*)-(+)-**2e** having a known configuration (vide infra).

(*S*)-(−)-1-Cyano-1-(1-naphthyl)methyl Acetate (3f). Prepared from 1-naphthaldehyde (**1f**). Flash column chromatography on silica gel eluting with [hexane (5):AcOEt (1)] and followed by rechromatography eluting with [hexane (12):AcOEt (1)] gave **3f** as a colorless crystalline solid: (805 mg, 36%); mp 48 °C; $[\alpha]_D^{25}$=−25.3 ° (*c* 1.02, $CHCl_3$); 69% e.e. [^{1}H NMR, with Eu(hfc)$_3$; δ(OAc) 2.47 (*R*) and 2.51 (*S*)]; IR (KBr) 2250 (C≡N) and 1760 (C=O) cm^{-1}; ^{1}H NMR δ=2.18 (3H, s, OAc), 7.03 (1H, s, CH), 7.47—7.68 (3H, m), 7.81 (1H, m), and 7.90—8.06 (3H, m); ^{13}C NMR δ=20.46 (CH_3CO), 61.31 (CH), 116.16 (C≡N), 122.59, 125.12, 126.63, 127.00, 127.63, 127.73, 129.19, 130.08, 131.54, 133.95, 169.05 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 225 (M$^+$, 25), 183 (23), 166 (57), 165 (100), 155 (18), 139 (17), 127 (17), and 43 (51); Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92; N, 6.22%. Found: C, 74.78; H, 4.92; N, 6.22%. The absolute configuration of (−)-**3f** was determined by comparing its optical rotation with that of the authentic sample (*R*)-(+)-**3f** derived from the optically active cyanohydrin (*R*)-(+)-**2f** with a known configuration (vide infra).

(*R*)-(+)-1-Cyano-1-(2-furyl)methyl Acetate (3g). Prepared from 2-furaldehyde (**1g**). Flash column chromatography on silica gel eluting with [hexane (6):AcOEt (1)] gave **3g** as a colorless oil: (822 mg, 42%); $[\alpha]_D^{25}$=+12.8 ° (*c* 1.02, $CHCl_3$); 47% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc) 2.56 (*R*) and 2.64 (*S*)]; IR (neat) 2250 (C≡N) and 1755 (C=O) cm^{-1}; ^{1}H NMR δ=2.16 (3H, s, OAc), 6.45 (1H, m, 4′-H), 6.47 (1H, s, CH), 6.69 (1H, m, 5′-H), and 7.51 (1H, m, 3′-H); ^{13}C NMR δ=20.26 (CH_3CO), 55.73 (CH), 111.13, 112.57, 114.16 (C≡N), 144.09, 145.04, and 168.75 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 165 (M$^+$, 18), 123 (25), 106 (62), 95 (8), 77 (33), 51 (20), 43 (58), 32 (29), and 16 (100); Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48%. Found: C, 58.45; H, 4.35; N, 8.67%. The absolute configuration of (+)-**3g** was determined by comparing its optical rotation with that of the authentic sample (*S*)-(−)-**3g** derived from the optically active cyanohydrin (*S*)-(+)-**2g** with a known configuration (vide infra).

(*S*)-(−)-1-Cyano-2-methylpropyl Acetate (3h). Prepared from 2-methylpropanal (**1h**). Flash column chromatography on silica gel eluting with [hexane (6):AcOEt (1)] gave **3h** as a colorless oil: (328 mg, 15%); $[\alpha]_D^{25}$=−60.6 ° (*c* 1.19, benzene); 69% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.67 (*R*) and 2.75 (*S*)]; IR (neat) 2250 (C≡N) and 1750 (C=O) cm^{-1}; ^{1}H NMR δ=1.09 (3H, d, *J*=7.0 Hz, CH_3), 1.12 (3H, d, *J*=6.8 Hz, CH_3), 2.04—2.28 (1H, m, C*H*(CH_3)$_2$), 2.16 (3H, s, OAc), and 5.18 (1H, d, *J*=5.6 Hz, C*H*(OAc)); ^{13}C NMR δ=17.32 (CH_3), 17.74 (CH_3), 20.33 (CH_3CO), 31.02 (*C*H(CH_3)$_2$), 66.31 (*C*H(OAc)), 115.98 (C≡N), and 169.20 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 141 (M$^+$, 0.3), 99 (78), 81 (17), 57 (67), 43 (100), 41 (35), and 39 (28). Found: *m*/*z* 141.07701. Calcd for $C_7H_{11}NO_2$: M, 141.07891; Anal. Calcd for $C_7H_{11}NO_2$: C, 59.56; H, 7.85; N, 9.92%. Found: C, 59.11; H, 7.85; N, 9.85%. The absolute configuration of (−)-**3h** was determined by comparing its optical rotation with that of the authentic sample (*R*)-(+)-**3h** derived from the optically active cyanohydrin (*R*)-(+)-**2h** with a known configuration (vide infra).

(*S*)-(−)-1-Cyanohexyl Acetate (3i). Prepared from hexanal (**1i**). Flash column chromatography on silica gel eluting with [hexane (15):AcOEt(1)] and followed by distillation [bp (bath temp) 128—129 °C/18 mmHg, 1 mmHg=133.322 Pa] gave **3i** as a colorless oil: (680 mg, 27%); $[\alpha]_D^{25}$=−47.5 ° (*c* 2.064, benzene) [lit,[6d] $[\alpha]_D$=+74 ° (*c* 2, benzene) for *R* isomer with 97% e.e.]; 75% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.31 (*R*) and 2.34 (*S*)]; IR (neat) 2250 (C≡N) and 1750 (C=O) cm^{-1}; ^{1}H NMR δ=0.91 (3H, m, CH_3), 1.20—1.59 (6H, m, 3×CH_2), 1.89 (2H, m, 2-CH_2), 2.14 (3H, s, OAc), and 5.31 (1H, t, *J*=6.8 Hz, CH); ^{13}C NMR δ=13.78 (CH_3), 20.30 (CH_3CO), 22.24, 24.12, 30.86, 32.13, 61.08 (CH), 116.91 (C≡N), and 169.14 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 169 (M$^+$, 0.3), 126 (22), 99 (25), 81 (100), 56 (38), 54 (28), 43 (62), and 41 (61). Found: *m*/*z* 169.10742. Calcd for $C_9H_{15}NO_2$: M, 169.11022; Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28%. Found: C, 63.44; H, 8.91; N, 8.25%.

(*R*)-(−)-1-Cyano-2-(1-naphthyloxy)ethyl Acetate (3j). Prepared from 2-(1-naphthyloxy)acetaldehyde (**1j**).[6a] Preparative thin-layer chromatography on silica gel developed with [hexane (4):AcOEt(1)] for 3 times gave **3j** as a slightly red solid: (106 mg, 28%); mp 54 °C; $[\alpha]_D^{23}$=−30.4 ° (*c* 1.67, $CHCl_3$) [lit,[6a] $[\alpha]_D^{23}$=+36.1 ° (*c* 1.19, $CHCl_3$) for *S* isomer with 87.4% e.e.]; 74% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.55 (*R*) and 2.61 (*S*)]; IR (neat) 2250 (C≡N) and 1755 (C=O) cm^{-1}; ^{1}H NMR δ=2.16 (3H, s, OAc), 4.41 (2H, d, *J*=5.2 Hz, OCH_2), 5.83 (1H, t, *J*=5.2 Hz, CH), 6.74 (1H, m), 7.35 (1H, m), 7.43—7.55 (3H, m), 7.80 (1H, m), and 8.23 (1H, m); ^{13}C NMR δ=20.33 (CH_3CO), 59.91 (OCH_2), 66.74 (CH), 105.32, 114.91 (C≡N), 121.76, 121.94, 125.35, 125.49, 125.85, 126.84, 127.55, 134.55, 153.25, and 168.97 (C=O); MS (70 eV) *m*/*z* (rel intensity %) 255 (M$^+$, 38), 213 (0.3), 194 (0.4), 157 (2), 144 (59), 127 (26), 115 (50), 112 (100), 89 (7), 77 (6), and 43 (87); Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49%. Found: C, 70.40; H, 5.10; N, 5.23%.

Stereochemical Correlation of Cyanohydrin Acetates. Preparation of Optically Active Cyanohydrins. In order to determine the absolute configuration of the acetates **3b**, **e**—**g**, and **h**, optically active cyanohydrins **2b**, **e**—**g**, and **h** were prepared by the kinetic resolution as shown below.

(*R*)-(+)-1-Hydroxy-1-(4-chlorophenyl)acetonitrile (2b). To an ethereal solution (80 mL) of 4-chlorobenzaldehyde (**1b**, 5.00 g, 35.57 mmol), was added an aqueous solution (40 mL) of KCN (4.63 g, 71.14 mmol) containing tetrabutylammonium bromide (11.6 mg, 0.36 mmol). Concentrated HCl (7.9 mL, 95 mmol) was added dropwise to the mixture with vigorous stirring over a period of 30 min 0 °C under an argon atmosphere and the mixture was stirred at 0 °C for 1.5 h and then at room temperature for 30 min. The ethereal phase was separated, washed with brine (30 mL) and dried (Na_2SO_4). Evaporation gave (±)-**2b** as a colorless oil: (5.82 g, 98%). The purity of (±)-**2b** was checked by ^{1}H NMR and immediately used for the next enzymatic reaction.

To a solution of (±)-**2b** (3.00 g, 17.89 mmol) and isopropenyl acetate (3.58 g, 35.78 mmol) in diisopropyl ether (60 mL), was added lipase from *Pseudomonas* sp. M-12-33 (Amano) (2.00 g), and the suspension was stirred at 40 °C for 47 h under an argon atmosphere. The lipase powder was filtered off and the filtrate was concentrated in vacuo to give an oil (3.39 g). ^{1}H NMR analysis showed that the resulting mixture contained 4-chlorobenzaldehyde **1b** (9%), the cyanohydrin **2b** (46%), and the acetate **3b** (45%).

t-Butyldimethylsilyl chloride (1.46 g, 9.66 mmol) was added to a solution of imidazole (1.37 g, 20.13 mmol) in DMF (20 mL) at 0 °C and stirred for 15 min. To this solution, was added the product mixture (3.08 g containing 1.35 g of **2b**, 8.05 mmol),

and the mixture was stirred overnight at room temperature. The reaction mixture was quenched with water (60 mL) and extracted with ether (2×30 mL). The combined extracts were washed with brine (20 mL) and dried (Na_2SO_4). Flash column chromatography on silica gel eluting with [hexane (20):AcOEt (1)] gave the *t*-butyldimethylsilyl ether as a colorless oil (1.79 g, 38% from (±)-**2b**): A small portion of the oil was further distilled for analysis: bp (bath temp) 120—121 °C/0.15 mmHg; $[\alpha]_D^{25}$=+11.9 ° (*c* 1.06, $CHCl_3$); ^{1}H NMR δ=0.15 and 0.23 (2×3H, 2×s, $Si(CH_3)_2$), 0.94 (9H, s, ^{t}Bu), 5.48 (1H, s, CH), and 7.35—7.47 (4H, m); ^{13}C NMR δ=−5.17 and −5.05 ($Si(CH_3)_2$), 18.19 ($SiC(CH_3)_3$), 25.54 ($C(CH_3)_3$), 63.40 (CH), 118.91 (C≡N), 127.49, 129.19, 135.06, and 135.28; Anal. Calcd for $C_{14}H_{20}ClNOSi$: C, 59.66; H, 7.15; N, 4.97%. Found: C, 59.90; H, 7.17; N, 5.14%.

t-Butyldimethylsilyl ether (500 mg, 1.88 mmol) was dissolved in a mixture of concentrated HCl (1 mL), AcOH (2 mL), and water (1 mL), and stirred at 40 °C for 3 h. The resulting mixture was evaporated in vacuo to remove AcOH. The residue was extracted with ether (3×10 mL) and dried (Na_2SO_4). Evaporation and crystallization from ether/light petroleum gave **2b** as needles (263.6 mg, 84%): mp 62 °C; $[\alpha]_D^{25}$=+24.3 ° (*c* 1.02, $CHCl_3$) [lit,[4e] $[\alpha]_D$=+27.2 ° (*c* 1.487, $CHCl_3$) for *R* isomer]; IR (KBr) 3400 (OH) and 2255 (C≡N) cm^{-1}; ^{1}H NMR δ=3.78 (1H, br s, OH), 5.50 (1H, s, CH), and 7.40 (4H, m); ^{13}C NMR δ=62.78 (CH), 118.62 (C≡N), 127.99, 129.37, 133.57, and 135.87; Anal Calcd for C_8H_6ClNO: C, 57.33; H, 3.61; N, 8.36%. Found: C, 57.07; H, 3.66; N, 8.33%. Acetylation of (*R*)-(+)-**2b** gave (*R*)-(−)-**3b**; $[\alpha]_D^{25}$=−36.3 ° (*c* 1.32, benzene); 81% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.70 (*R*) and 2.79 (*S*)].

(*R*)-(+)-1-Hydroxy-1-(2-naphthyl)acetonitrile (2e). Crystallization from ether–hexane afforded fine needles; mp 117 °C; $[\alpha]_D^{25}$=+22.0 ° (*c* 1.02, $CHCl_3$) [lit,[4e] $[\alpha]_D$=+26.4 ° (*c* 0.522, $CHCl_3$) for *R* isomer with 86% e.e.]; IR (KBr) 3430 (OH) and 2250 (C≡N) cm^{-1}; ^{1}H NMR δ=2.64 (1H, br s, OH), 5.70 (1H, s, CH), 7.50—7.62 (3H, m), and 7.81—8.02 (4H, m); ^{13}C NMR δ=63.83 (CH), 118.78 (C≡N), 123.65, 126.20, 126.96, 127.25, 127.81, 128.34, 129.38, 132.42, 132.93, and 133.68; Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65%. Found: C, 78.91; H, 5.02; N, 7.44%. Acetylation of (*R*)-(+)-**2e** gave (*R*)-(−)-**3e**; $[\alpha]_D^{25}$=−16.0 ° (*c* 1.05, $CHCl_3$); 68% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.80 (*R*) and 2.87 (*S*)].

(*R*)-(+)-1-Hydroxy-1-(1-naphthyl)acetonitrile (2f). Crystallization from ether–light petroleum gave fine needles; mp 77 °C; $[\alpha]_D^{25}$=+9.5 ° (*c* 1.17, $CHCl_3$) [lit,[30] $[\alpha]_D$=+48.0 ° (*c* 1.325, $CHCl_3$) for *R* isomer with 73% e.e.]; IR (KBr) 3380 (OH) and 2250 (C≡N) cm^{-1}; ^{1}H NMR δ=3.54 (1H, br s, OH), 6.02 (1H, s, CH), 7.37—7.59 (3H, m), 7.71 (1H, m), 7.82—7.88 (2H, m), and 8.02 (1H, m); ^{13}C NMR δ=62.00 (CH), 118.90 (C≡N), 122.89, 125.10, 125.61, 126.46, 127.28, 128.97, 129.90, 130.23, 130.79, and 133.88; Anal. Calcd for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65%. Found: C, 78.88; H, 4.97; N, 7.64%. Acetylation of (*R*)-(+)-**2f** gave (*R*)-(+)-**3f**; $[\alpha]_D^{25}$=+5.1 ° (*c* 1.17, $CHCl_3$); 15% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.39 (*R*) and 2.42 (*S*)].

(*S*)-(+)-1-Hydroxy-1-(2-furyl)acetonitrile (2g). Optically active TBDMS-ether of cyanohydrin was prepared from 2-furaldehyde (**1g**) by the same procedure as described for **2b**. Flash column chromatography on silica gel eluting with [hexane:AcOEt=30:1 to 15:1] afforded *t*-butyldimethylsilyl ether as a colorless oil (2.67 g, 48% from (±)-**2g**): $[\alpha]_D^{25}$=+9.5 (*c* 1.02, $CHCl_3$); ^{1}H NMR δ=0.14 and 0.17 (2×3H, 2×s, $Si(CH_3)_2$), 0.92 (9H,s, ^{t}Bu), 5.56 (1H, s, CH), 6.40 (1H, dd, *J*=3.4 and 1.8 Hz, 4′-H), 6.53 (1H, dt, *J*=3.4 and 0.8 Hz, 3′-H), and 7.45 (1H, dd, *J*=1.8 and 0.8 Hz, 5′-H); ^{13}C NMR δ=−5.24 ($SiCH_3$), 18.17 ($SiC(CH_3)_3$), 25.45 ($C(CH_3)_3$), 58.08 (CH), 109.43, 110.76, 117.23 (C≡N), 143.77, and 148.51; Anal. Calcd for $C_{12}H_{19}NO_2Si$: C, 60.72; H, 8.07; N, 5.90%. Found: C, 60.56; H, 8.33; N, 6.00%.

Acid deprotection of (+)-TBDMS-ether gave **2g** as a colorless oil; $[\alpha]_D^{20}$=+23.29 ° (neat) [lit,[1] $[\alpha]_D^{20}$=+30.6 ° (neat) for *S* isomer]; IR (neat) 3380 (OH) and 2250 (C≡N) cm^{-1}; ^{1}H NMR δ=4.04 (1H, br s, OH), 5.53 (1H, s, CH), 6.40 (1H, dd, *J*=3.4 and 1.8 Hz, 4′-H), 6.57 (1H, d, *J*=3.4 Hz, 3′-H), and 7.46 (1H, dd, *J*=1.8 and 0.8 Hz, 5′-H); ^{13}C NMR δ=56.79 (CH), 110.19, 110.93, 117.09 (C≡N), 144.35, and 147.44; Anal. Calcd for $C_6H_5NO_2$: C, 58.54; H, 4.09; N, 11.38%. Found: C, 58.78; H, 4.27; N, 11.14%. Acetylation of (*S*)-(+)-**2g** gave (*S*)-(−)-**3g**; $[\alpha]_D^{25}$=−14.4 ° (*c* 1.05, $CHCl_3$); 60% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.46 (*R*) and 2.49 (*S*)].

(*R*)-(+)-1-Hydroxy-2-methylpropanenitrile (2h). Flash column chromatography on silica gel eluting with [hexane: AcOEt=8:1 to 5:1] afforded a colorless oil; $[\alpha]_D^{25}$=+2.6 ° (*c* 1.12, $CHCl_3$) [lit,[4e] $[\alpha]_D$=+2.7 ° (*c* 3.908, $CHCl_3$) for *R* isomer with 17% e.e.]; IR (neat) 3400 (OH) and 2250 (C≡N) cm^{-1}; ^{1}H NMR δ=1.06 (3H, d, *J*=5.8 Hz, CH_3), 1.09 (3H, d, *J*=5.6 Hz, CH_3), 2.04 (1H, m, CH), 3.73 (1H, br s, OH), and 4.28 (1H, d, *J*=6.0 Hz, C*H*(OAc)); ^{13}C NMR δ=17.21 (CH_3), 17.66 (CH_3), 32.97 ($CH(CH_3)_2$), 66.87 (*C*H(OAc)), and 119.33 (C≡N); Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13%. Found: C, 60.50; H, 9.32; N, 13.97%. Acetylation of (*R*)-(+)-**2h** gave (*R*)-(+)-**3h**; $[\alpha]_D^{25}$=+11.8 ° (*c* 1.31, benzene); 14% e.e. [^{1}H NMR using Eu(hfc)$_3$; δ(OAc)=2.58 (*R*) and 2.65 (*S*)].

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