Efficient Lipase-Catalyzed Kinetic Resolution and Dynamic Kinetic Resolution of β-Hydroxy Nitriles. A Route to Useful Precursors for γ-Amino Alcohols

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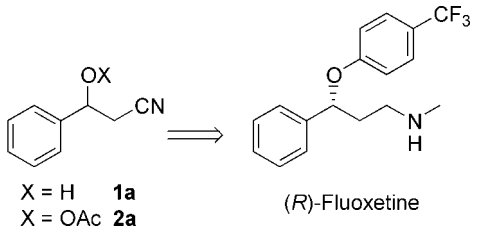
Abstract: An efficient kinetic resolution of racemic β-hydroxy nitriles **1** was performed *via Candida antarctica* lipase (N-435)-catalyzed transesterification. A variety of racemic alkyl, aryl, and aryloxymethyl substituted β-hydroxy nitriles was efficiently transformed to the corresponding enantiomerically pure acetates (ee > 99% and conversion = 50%) with *E* values from 40 to >1000. The combination of the enzymatic kinetic resolution with a ruthenium-catalyzed alcohol racemization led to a dynamic kinetic resolution (ee's up to 99%, yields up to 85%).

Keywords: dynamic kinetic resolution; β-hydroxy nitriles; kinetic resolution; lipases; ruthenium

Introduction

The importance of optically active amino alcohols as versatile building blocks in both asymmetric synthesis[1] and medicinal chemistry[2] is well established. Many approaches have been developed to obtain chiral β-amino alcohols from an achiral substrate.[3] However, few approaches exist for the preparation of chiral γ-amino alcohols, and of the methods known, bioconversions have had a dominant role. In particular, the microbial reduction of β-keto esters has been widely applied.[4] The reduction of β-keto amides[5] and β-keto nitriles[6] also provides access to γ-amino alcohols, but to a more limited extent. For example, the bioreduction of α-unsubstituted β-keto nitriles usually results in low chemical yields, due to the existence of a competing α-ethylation reaction.[6] Another alternative route reported for the preparation of γ-amino alcohols is the lipase-catalyzed hydrolysis of β-acetoxy nitriles.[7] However, to obtain good reaction rates and enantioselectivity, additives such as catalytic amounts of thiacrown ether, were required.[7]

Following our investigations dealing with bioconversions,[3g,8] we now report on a highly efficient kinetic resolution of β-hydroxy nitriles **1** *via* lipase-catalyzed esterification. This procedure is applied to the resolution of different alkyl-, aryl-, and aryloxymethyl-substituted nitrile alcohol derivatives, which are important precursors of biologically active compounds, e.g., the antidepressant fluoxetine can be easily prepared from acetoxy nitrile **2a** or its corresponding hydroxy nitrile **1a** (Scheme 1).[9]



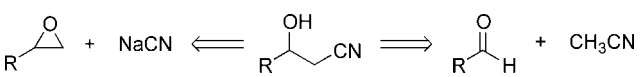
Scheme 1.

We also report on the combination of the enzymatic kinetic resolution with ruthenium-catalyzed alcohol racemization, which leads to a useful dynamic kinetic resolution.

Results and Discussion

Synthesis of β-Hydroxy Nitriles

For the synthesis of starting materials, two different routes were employed (Scheme 2). Thus, substrates **1a – f** were prepared efficiently by reaction of cyanomethyllithium, generated *in situ* by deprotonation of acetonitrile by BuLi, with the corresponding aldehyde.[7] Substrates **1g – k** were obtained from ring-opening of the corresponding epoxide by sodium cyanide using standard conditions.[10]



Scheme 2. Preparation of β-hydroxy nitriles **1a – k**.

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Kinetic Resolution Experiments

In a first set of experiments, the efficiency of different commercially available lipases to catalyze the transesterification of chiral β-hydroxy nitriles **1** was investigated. For this purpose, racemic 3-hydroxy-3-phenylpropanenitrile (**1a**) was chosen as model substrate and treated at room temperature with three equivalents of *p*-chlorophenyl acetate (**3**) in toluene in the presence of different lipases. In a control experiment, it was shown that the reaction did not proceed in the absence of enzyme. Some results are shown in Table 1. In all the cases, the enantioselectivity was excellent. At room temperature, the activities were much better for *Pseudomonas cepacia* lipases (entries 2 and 3). As expected, both PS-D and PS-C enzymes proceed similarly, since they only differ in the immobilization. The other examined lipases (lipase from porcine pancreas, *Candida rugosa*, and *Aspergillus* sp.) showed no reaction after 48 h.

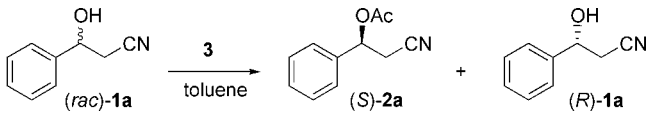
The high thermostability of lipase N-435 in organic solvents, however, allowed us to obtain also the combination of good activity and enantioselectivity at 60 °C (entry 5).[3g,11] At this temperature, *Pseudomonas cepacia* lipase showed lower enantioselectivity (around 85% ee in **2a** at 20% conversion, $E \sim 20$).

It is well known that enantioselectivity and reaction rates in the kinetic resolutions by lipases can be greatly influenced by variation of solvent and acyl donor.[12] We therefore screened for the N-435-catalyzed transesterification of *rac*-**1a** with different solvents and acyl donors. The results are given in Table 2.

First, we studied the acetylation of *rac*-**1a** with *p*-chlorophenyl acetate (**3**) at 60 °C in the presence of lipase N-435 in various non-polar solvents (entries 1 – 5). The results showed that the reaction rates are very dependent on the solvent. Thus, the best activity was observed in toluene, while the acetylation in ethers and cyclohexane proceeded with significantly slower reaction rates.

Next, a series of different acyl donors were screened using toluene as a solvent (entries 5 – 9). As has been previously observed in the kinetic resolu-

Table 1. Lipase-catalyzed kinetic resolution of *rac*-**1a**.[a]



Entry	Lipase	Time (h)	Rate[b]	% Conversion	% ee **2a**[c]	% ee **1a**[c]
1	*Pseudomonas fluorescens*	48	0.6	29	> 99	41
2	*Pseudomonas cepacia* (PS-D)	24	8.8	50	> 99	> 99
3	*Pseudomonas cepacia* (PS-C)	24	8.8	50	> 99	> 99
4	*Candida antarctica* B (N-435)	48	0.6	29	> 99	41
5[d]	*Candida antarctica* B (N-435)	24	13.2	50	> 99	> 99

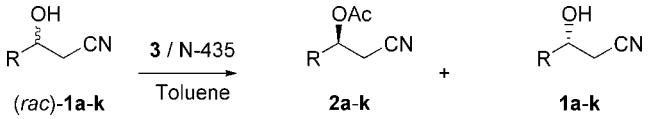
[a] Conditions: 0.1 mmol of *rac*-**1a**, 0.3 mmols of **3**, 5 mg of enzyme, and 1 mL toluene at 22 °C.
[b] Initial rate.
[c] Enantiomeric excess determined by GC.
[d] 10 mg of N-435 at 60 °C.

Table 2. Kinetic resolution of *rac*-**1a** with *Candida antarctica* lipase B (N-435) using different solvents and acyl donors.[a]

Entry	Solvent	Acyl donor[b]	Time (h)	Rate[c]	% Conversion	% ee **2a**[d]	% ee **1a**[d]
1	*t*-BuOMe	**3**	24	3.3	44	> 99	82
2	$(i\text{-Pr})_2O$	**3**	24	5.7	49	> 99	98
3	$(n\text{-Bu})_2O$	**3**	24	2.9	32	> 99	64
4	Cyclohexane	**3**	24	nd	5	> 99	2
5	Toluene	**3**	24	13.2	50	> 99	> 99
6	Toluene	**4**	24	5.2	40	> 99	62
7	Toluene	**5**	24	8.5	49	> 99	98
8	Toluene	**6**	24	0.8	20	> 99	27
9	Toluene	**7**	24	0.6	15	> 99	22

[a] Conditions: 0.1 mmol of *rac*-**1a**, 0.3 mmol of acyl donor, 1 mL of solvent, and 10 mg of *Candida antarctica* lipase B (N-435) at 60 °C.
[b] **3** = *p*-chlorophenyl acetate, **4** = vinyl acetate, **5** = isopropenyl acetate, **6** = ethyl acetate, **7** = 2,2,2-trifluoroethyl acetate.
[c] Initial rate.
[d] Enantiomeric excess determined by GC.
[d] Enantiomeric ratio.

Table 3. Lipase-catalyzed kinetic resolution of *rac*-**1**.[a]



(*rac*)-**1a-k** **2a-k** **1a-k**

Entry	Substrate	R	Time (h)	% Conversion of **1**[b]	% ee of **2**[c]	% ee of **1**[c]	E[d]
1	**1a**	Ph	24	50	> 99 (*S*)	> 99 (*R*)	> 1000
2	**1b**	*p*-MeO-C_6H_4	16	50	> 99 (*S*)	> 99 (*R*)	> 1000
3	**1c**	*p*-NO_2-C_6H_4	12	50	> 99 (*S*)	> 99 (*R*)	> 1000
4	**1d**	2-Naphthyl	36	50	99 (*S*)	> 99 (*R*)	> 1000
5[e]	**1e**	2-Furyl	60	43	89 (*S*)	77 (*R*)	40±1
6	**1f**	3-Pyridyl	20	51	97 (*S*)	> 99 (*R*)	220±10
7	**1g**	Benzyl	6	49	91 (*R*)	88 (*S*)	61±2
8[e]	**1h**	$PhOCH_2$	6	52	95 (*S*)	99 (*R*)[f]	197±7
9[e]	**1i**	1-Naphthyl-OCH_2	3	49	96 (*S*)	98 (*R*)	225±15
10	**1j**	Cyclohexyl	36	49	> 99 (*S*)	97 (*R*)	840±40
11	**1k**	CH_3-$(CH_2)_7$-	6	51	94 (*R*)	98 (*S*)	148±6

[a] Conditions: 0.2 mmol of *rac*-**1**, 0.6 mmol of **3**, 20 mg of *Candida antarctica* lipase B (N-435), and 2 mL toluene at 60 °C.
[b] % Conversion measured by NMR.
[c] Enantiomeric excess determined by GC or HPLC. Absolute configuration shown in parenthesis.
[d] Enantiomeric ratio.
[e] T = 30 °C.
[f] Enantiomeric excess determined by derivatization of **1** to the corresponding acetate **2**.

tion of azido alcohols,[13] the N-435-catalyzed transesterification proceeds faster with isopropenyl acetate (**5**) than with vinyl acetate (**4**) (entry 7 vs. 6). However, the best activity was obtained with the *p*-chlorophenyl acetate (**3**) (entry 5). Moreover, using ethyl acetate (**6**) and 2,2,2-trifluoroethyl acetate (**7**) the reaction proceeds around 15 times slower than that with the use of **3** (entries 8 and 9 vs. 5).

We then applied this new procedure to a series of β-hydroxy nitriles. The results are given in Table 3. The kinetic resolution of various 3-hydroxy-3-phenylpropanenitrile derivatives **1a – c** gave 50% conversion in more than 99% ee in both starting materials **1** and products **2** (Table 3, entries 1 – 3). These results further indicate that the presence of different substituents in the *para* position of the aromatic ring does not significantly influence the enantiomeric ratio (E) and therefore the efficiency of the process. The kinetic resolution of the 3-naphthyl derivative **1d** under these conditions also gave excellent enantiomeric ratios (entry 4). Using this procedure heteroaromatic compounds **1e** and **1f** were also efficiently kinetically resolved, however with lower enantiomeric ratios, especially in the case of the 2-furyl derivative **1e** (entry 5).

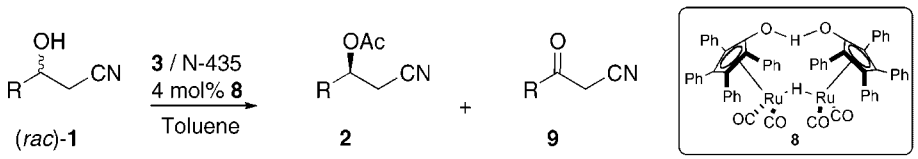
For the benzyl derivative **1g** the enantiomeric ratio is 61. For the aryloxymethyl derivatives **1h** and **1i**, the kinetic resolution under the "standard conditions" used (i.e., 100 mg N-435/mmol product, 60 °C) gave a low enantioselectivity. This behavior has also been observed in the N-435-catalyzed transesterification of closely related 1-azido-2-hydroxy-3-aryloxypropane derivatives.[13] However, the enantiomeric ratios for **1h** and **1i** can be substantially improved if the reaction is carried out at a lower temperature (entries 8 and 9). The kinetic resolution of alkyl derivatives **1j** and **1k** also proceed with excellent enantioselectivity (entries 10 and 11). Recently, and while this manuscript was in preparation, Kamal et al. have published the kinetic resolution of some aryloxypropane derivatives using *Pseudomonas cepacia* lipase (PS-C) with good enantioselectivity but with long reaction times (e.g., 98 hours for **1h**).[14]

Dynamic Kinetic Resolution Experiments

We have recently developed various dynamic kinetic resolution (DKR) processes by combining enzymatic resolution with ruthenium-catalyzed isomerization of the alcohol.[3g,11] Initial attempts to obtain a DKR of β-hydroxy nitriles **1** at 60 – 70 °C were unsuccessful.[15] Finally, we found that running the reaction at 100 °C with lipase N-435, acyl donor **3** and ruthenium catalysts **8** gave a dynamic kinetic resolution with yields up to 85% and with ee's in the range of 94% to 99%. The results are summarized in Table 4.

In all cases, the corresponding ketone **9**, formed during the hydrogen transfer process, was observed. The formation of ketone can be partly overcome by adding a hydrogen source such as 2,4-dimethyl-3-pentanol (entry 2 vs. entry 1).[16] The DKR of various 3-hydroxy-3-arylpropanenitriles **1a – d** gave good yields and high enantioselectivity (Table 4, entries 2 – 5).

Table 4. Dynamic kinetic resolution (DKR) of *rac*-**1**.[a]



Entry	Substrate	R	Time (h)	% of **2**[b]	% ee of **2**[c]	% of **9**[b]
1	**1a**	Ph	36	74	97 (*S*)	23
2[d]	**1a**	Ph	36	85	97 (*S*)	11
3	**1b**	*p*-MeO-C_6H_4	36	81	99 (*S*)	19
4	**1c**	*p*-NO_2-C_6H_4	36	72	96 (*S*)	26
5	**1d**	2-Naphthyl	36	78	94 (*S*)	21

[a] Conditions: 0.2 mmol of *rac*-**1a**, 0.6 mmol of **3**, 20 mg of *Candida antarctica* lipase B (N-435), 4 mol % of **8**, and 2 mL toluene at 100 °C.
[b] % Yield measured by NMR.
[c] Optical purity measured by GC or HPLC. Absolute configuration shown in parenthesis.
[d] 0.1 mmol of 2,4-dimethyl-3-pentanol added.

Conclusion

A highly efficient lipase-catalyzed kinetic resolution of racemic β-hydroxy nitriles **1** has been developed employing inexpensive *Candida antarctica* lipase B (N-435). It was demonstrated that the resolution can be turned into a dynamic kinetic resolution process by the use of an alcohol racemization catalyst. The enantiomerically pure β-hydroxy nitriles are versatile synthetic intermediates and important precursors for biologically active γ-amino alcohols.

Experimental Section

General Remarks

All reactions were carried out under a dry argon atmosphere. Solvents were purified by standard procedures. Solvents for HPLC use were spectrometric grade. *p*-Chlorophenyl acetate **3**[8b] and Ru-catalyst **8**[8d] were prepared according to literature procedures. All other reagents are commercially available and were used without further purification. Novozym-435 (N-435) was a generous gift from Novo Nordisk A/S, Denmark. Lipase PS-C and PS-D were generous gifts from Amano Pharmaceutical Co. Ltd, Japan. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. Solvents for extraction and chromatography were technical grade and distilled before use. Column chromatography was performed with Merck 60 silica gel. The enantiomeric excesses of compounds **1c**, **2c**, **1d**, **2d**, **1f**, **2f** were determined by analytical HPLC employing a Daicel, Chiracel OD-H column using racemic compounds as references. The flow parameters were: *n*-hexane:*iso*-propanol = 60:40, 0.5 mL/min, 254 nm. The enantiomeric excess of all the other compounds was determined by GC analysis on a CP-Chirasil-Dex CB column using racemic compounds as references. The oven parameters were: 110 °C for 30 min and then 5 °C/min up to 200 °C.

General Procedure for the Preparation of β-Hydroxy Nitriles from Aromatic Aldehyde and Acetonitrile: 3-Hydroxy-3-phenylpropanenitrile (1a)

To a solution of isopropylamine (1.44 mL, 10 mmol) in THF (10 mL) under an argon atmosphere at –78 °C was added a solution of *n*-BuLi in hexane (1.6 M, 6.25 mL, 10 mmol). After 20 min, a solution of acetonitrile (470 μL, 9 mmol) in THF (5 mL) was added. The mixture was stirred for 30 min at –78 °C, and then a solution of benzaldehyde (0.91 mL, 9 mmol) in THF (5 mL) was added and the reaction was stirred at –78 °C for 3 hours. The reaction was quenched with saturated ammonium chloride (25 mL). The mixture was extracted with diethyl ether (3 × 50 mL), the combined ether phases were dried over Na_2SO_4 and evaporated. The residue was purified by chromatography to give alcohol **1a** as a colorless oil; yield: 1.21 g (92%). The NMR data are in agreement with those previously reported.[7a] GC retention times: 44.6 (*S*), 45.0 (*R*).

3-Hydroxy-3-(*p*-methoxyphenyl)-propanenitrile (1b): Yield: 1.35 g (85%). The NMR data are in agreement with those previously reported.[17] GC retention times: 48.4 (*S*), 48.8 (*R*).

3-Hydroxy-3-(*p*-nitrophenyl)-propanenitrile (1c): Yield: 1.23 g (72%). ^{1}H NMR: δ = 2.81 (m, 2H, CH_2), 5.19 (t, 1H, CH, $^3J_{H,H}$ = 6.0 Hz), 7.61 (d, 2H, CH=, $^3J_{H,H}$ = 7.8 Hz), 8.28 (d, 2H, CH=, $^3J_{H,H}$ = 7.8 Hz); ^{13}C NMR: δ = 28.3 (CH_2), 69.4 (CH), 116.3 (CN), 124.4 (CH=), 126.8 (CH=), 131.3 (C), 147.8 (C). HPLC retention times: 11.0 (*R*), 12.0 (*S*).

3-Hydroxy-3-(2-naphthyl)-propanenitrile (1d): Yield: 1.61 g (91%). ^{1}H NMR: δ = 2.79 (m, 2H, CH_2), 3.12 (b, 1H, OH), 5.12 (t, 1H, CH, $^3J_{H,H}$ = 6.0 Hz), 7.45 (dd, 1H, CH=, $^3J_{H,H}$ = 8.4 Hz, $^3J_{H,H}$ = 1.6 Hz), 7.50 (m, 2H, CH=), 7.83 (m, 4H, CH=). ^{13}C NMR: δ = 28.1 (CH_2), 70.3 (CH), 117.7 (CN), 123.3 (CH=), 124.9 (CH=), 126.7 (CH=), 126.8 (CH=), 128.0 (CH=), 128.3 (CH=), 129.0 (CH=), 133.3 (C), 133.6 (C), 138.7 (C). HPLC retention times: 16.5 (*R*), 17.8 (*S*).

3-Hydroxy-3-(2-furyl)-propanenitrile (1e): Yield: 0.94 g (76%). ^{1}H NMR: δ = 2.89 (m, 2H, CH_2), 5.04 (t, 1H, CH, $^3J_{H,H}$ = 6.6 Hz), 6.38 (m, 2H, CH=), 7.41 (m, 1H, CH=);

^{13}C NMR: δ = 25.1 (CH_2), 64.0 (CH), 107.7 (CH=), 110.8 (CH=), 117.2 (CN), 143.2 (C). GC retention times: 40.3 (*S*), 40.6 (*R*).

3-Hydroxy-3-(3-pyridyl)-propanenitrile (1f): Yield: 1.04 g (78%). ^{1}H NMR: δ = 2.78 (m, 2H, CH_2), 5.07 (t, 1H, CH, $^3J_{H,H}$ = 6.0 Hz), 5.2 (br, 1H, OH), 7.32 (dd, 1H, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 4.8 Hz), 7.82 (dt, 1H, $^3J_{H,H}$ = 8.4 Hz, $^3J_{H,H}$ = 2.0 Hz), 8.41 (dd, 1H, $^3J_{H,H}$ = 4.8 Hz, $^3J_{H,H}$ = 1.2 Hz), 8.48 (d, 1H, $^3J_{H,H}$ = 2.4 Hz); ^{13}C NMR: δ = 28.3 (CH_2), 67.5 (CH), 117.4 (CN), 124.3 (CH=), 134.4 (CH=), 137.9 (C), 147.1 (CH=), 149.4 (CH=). HPLC retention times: 12.0 (*R*), 17.8 (*S*).

General Procedure for the Preparation of β-Hydroxy Nitriles from Epoxides: 3-Hydroxy-3-benzylpropanenitrile (1g)

A solution of benzyloxirane (1.34 g, 10 mmol), NaCN (2.5 g, 50 mmol) and ammonium chloride (1.17 g, 20 mmol) in MeOH/H_2O (89 mL/11 mL) was stirred at 85 °C during 15 hours. Then, methanol was evaporated. The residue was extracted with CH_2Cl_2 (3 × 50 mL) and dried over Na_2SO_4 to give alcohol **1g** as a yellow oil; yield: 1.45 g (90%). ^{1}H NMR: δ = 2.52 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.0 Hz), 2.57 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 5.2 Hz), 2.88 (dd, 1H, CH_2-Ph, $^3J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 7.6 Hz), 2.93 (dd, 1H, CH_2-Ph, $^3J_{H,H}$ = 13.6 Hz, $^3J_{H,H}$ = 5.6 Hz), 4.16 (m, 1H, CH), 7.30 (m, 5H, CH=); ^{13}C NMR: δ = 25.4 (CH_2-CN), 43.0 (CH_2-Ph), 68.6 (CH), 117.1 (CN), 127.5 (CH=), 129.1 (CH=), 129.5 (CH=), 132.3 (C). GC retention times: 44.3 (*S*), 44.6 (*R*).

3-Hydroxy-4-phenoxybutanenitrile (1h): Yield: 1.52 g (86%). ^{1}H NMR: δ = 2.70 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.3 Hz), 2.79 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.0 Hz), 4.06 (m, 2H, CH_2-O), 4.33 (m, 1H, CH), 6.90 (m, 2H, CH=), 7.03 (m, 1H, CH=), 7.29 (m, 2H, CH=); ^{13}C NMR: δ = 22.8 (CH_2-CN), 66.5 (CH_2-O), 70.0 (CH), 114.7 (CH=), 116.7 (CN), 122.0 (CH=), 129.9 (CH=), 156.3 (C).

3-Hydroxy-4-(1-naphthoxy)-butanenitrile (1i): Yield: 1.70 g (75%). ^{1}H NMR: δ = 2.79 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.3 Hz), 2.88 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 5.7 Hz), 4.23 (m, 2H, CH_2-O), 4.48 (m, 1H, CH), 6.82 (d, 1H, CH=, $^3J_{H,H}$ = 7.5 Hz), 7.37 (m, 1H, CH=), 7.50 (m, 3H, CH=) 7.82 (m, 1H, CH=), 8.19 (m, 1H, CH=); ^{13}C NMR: δ = 23.1 (CH_2-CN), 66.7 (CH_2-O), 70.4 (CH), 105.4 (CH=), 117.2 (CN), 121.7 (CH=), 125.5 (CH=), 125.8 (CH=), 125.9 (CH=), 126.9 (CH=), 127.9 (CH=), 134.7 (C), 153.7 (C). HPLC retention times: 16.5 (*S*), 17.8 (*R*).

3-Hydroxy-3-cyclohexylpropanenitrile (1j): Yield: 1.28 g (84%). The NMR data are in agreement with those previously reported.[7c] GC retention times: 43.1 (*S*), 43.2 (*R*).

3-Hydroxyundecanenitrile (1k): Yield: 1.48 g (81%). The NMR data are in agreement with those previously reported.[7c] GC retention times: 44.0 (*R*), 44.2 (*S*).

General Procedure for the Preparation of β-Acetoxy Nitriles: 2-Cyano-1-phenylethyl Acetate (2a)

To a solution of **1a** (147.2 mg, 1 mmol) in dichloromethane (5 mL), triethylamine (1 mL) and acetic anhydride (5 mmol) were added at 0 °C. The reaction was then stirred at room temperature overnight. The mixture was then evaporated and the residue purified by chromatography to give acetate **2a** as a colorless oil; yield: 176 mg (93%). The NMR data are in agreement with those previously reported.[7a] GC retention times: 39.2 (*R*), 39.5 (*S*).

2-Cyano-1-(*p*-methoxyphenyl)ethyl Acetate (2b): The NMR data are in agreement with those previously reported.[17] GC retention times: 45.6 (*R*), 45.7 (*S*).

2-Cyano-1-(*p*-nitrophenyl)ethyl Acetate (2c): ^{1}H NMR: δ = 2.19 (s, 3H, CH_3), 2.89 (dd, 1H, CH_2, $^3J_{H,H}$ = 17.2 Hz, $^3J_{H,H}$ = 6.0 Hz), 2.98 (dd, 1H, CH_2, $^3J_{H,H}$ = 17.2 Hz, $^3J_{H,H}$ = 5.6 Hz), 6.04 (t, 1H, CH, $^3J_{H,H}$ = 6.0 Hz), 7.59 (d, 2H, CH=, $^3J_{H,H}$ = 8.8 Hz), 8.27 (d, 2H, CH=, $^3J_{H,H}$ = 8.8 Hz); ^{13}C NMR, δ: 21.0 (CH_3), 25.6 (CH_2), 69.7 (CH), 115.4 (CN), 124.5 (CH=), 127.4 (CH=), 129.1 (C), 144.0 (C), 169.5 (CO). HPLC retention times: 17.7 (*R*), 21.2 (*S*).

2-Cyano-1-(2-naphthyl)ethyl Acetate (2d): ^{1}H NMR: δ = 2.18 (s, 3H, CH_3), 2.99 (m, 2H, CH_2), 6.14 (t, 1H, CH, $^3J_{H,H}$ = 6.0 Hz), 7.47 (dd, 1H, CH=, $^3J_{H,H}$ = 8.7 Hz, $^3J_{H,H}$ = 2.1 Hz), 7.52 (m, 2H, CH=), 7.87 (m, 4H, CH=); ^{13}C NMR, δ: 21.2 (CH_3), 25.7 (CH_2), 70.9 (CH), 116.3 (CN), 123.4 (CH=), 126.0 (CH=), 126.9 (CH=), 127.0 (CH=), 128.0 (CH=), 128.4 (CH=), 129.3 (CH=), 133.2 (C), 133.7 (C), 134.6 (C), 169.9 (CO). HPLC retention times: 23.9 (*R*), 42.6 (*S*).

2-Cyano-1-(2-furyl)ethyl Acetate (2e): ^{1}H NMR: δ = 2.15 (s, 3H, CH_2), 2.99 (dd, 1H, CH_2, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.0 Hz), 3.08 (dd, 1H, CH_2, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.9 Hz), 6.06 (t, 1H, CH, $^3J_{H,H}$ = 6.3 Hz), 6.38 (m, 1H, CH=), 6.49 (m, 1H, CH=), 7.42 (m, 1H, CH=); ^{13}C NMR: δ = 20.9 (CH_3), 22.3 (CH_2), 63.9 (CH), 110.3 (CH=), 110.9 (CH=), 115.9 (CN), 143.6 (CH=), 149.2 (C), 169.8 (CO). GC retention times: 31.4 (*R*), 32.2 (*S*).

2-Cyano-1-(3-pyridyl)ethyl Acetate (2f): ^{1}H NMR: δ = 2.16 (s, 3H, CH_3), 2.90 (dd, 1H, CH_2, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.0 Hz),), 2.96 (dd, 1H, CH_2, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.8 Hz), 5.99 (t, 1H, CH, $^3J_{H,H}$ = 6.4 Hz), 7.34 (dd, 1H, $^3J_{H,H}$ = 7.6 Hz, $^3J_{H,H}$ = 4.4 Hz), 7.76 (dt, 1H, $^3J_{H,H}$ = 8.0 Hz, $^3J_{H,H}$ = 1.6 Hz), 8.62 (dd, 1H, $^3J_{H,H}$ = 5.2 Hz, $^3J_{H,H}$ = 2.0 Hz), 8.64 (d, 1H, $^3J_{H,H}$ = 2.0 Hz); ^{13}C NMR: δ = 21.0 (CH_3), 25.6 (CH_2), 68.6 (CH), 115.7 (CN), 123.9 (CH=), 133.0 (C), 134.2 (CH=), 148.0 (CH=), 147.9 (C), 147.1 (CH=), 150.8 (CH=), 169.6 (CO). HPLC retention times: 24.1 (*R*), 25.9 (*S*).

2-Cyano-1-benzylethyl Acetate (2g): ^{1}H NMR: δ = 2.09 (s, 3H, CH_3), 2.50 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 17.1 Hz, $^3J_{H,H}$ = 4.8 Hz), 2.65 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 17.1 Hz, $^3J_{H,H}$ = 4.8 Hz), 2.94 (dd, 1H, CH_2-Ph, $^3J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 7.8 Hz), 3.12 (dd, 1H, CH_2-Ph, $^3J_{H,H}$ = 14.1 Hz, $^3J_{H,H}$ = 6.4 Hz), 5.17 (m, 1H, CH), 7.30 (m, 5H, CH=). ^{13}C NMR: δ = 21.1 (CH_3), 22.2 (CH_2-CN), 39.4 (CH_2-Ph), 69.7 (CH), 116.4 (CN), 127.5 (CH=), 129.1 (CH=), 129.5 (CH=), 135.5 (C), 170.3 (CO). GC retention times: 41.1 (*S*), 41.5 (*R*).

2-Cyano-1-phenoxymethylethyl Acetate (2h): ^{1}H NMR: δ = 2.14 (s, 3H, CH_3), 2.87 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 6.0 Hz), 2.93 (dd, 1H, CH_2-CN, $^3J_{H,H}$ = 16.8 Hz, $^3J_{H,H}$ = 5.6 Hz), 4.12 (dd, 1H, CH_2-O, $^3J_{H,H}$ = 9.6 Hz, $^3J_{H,H}$ = 5.6 Hz), 4.18 (dd, 1H, CH_2-O, $^3J_{H,H}$ = 9.6 Hz, $^3J_{H,H}$ = 4.4 Hz), 5.33 (m, 1H, CH), 6.92 (d, 2H, CH=, $^3J_{H,H}$ = 7.6 Hz), 7.03 (m, 1H, CH=), 7.31 (m, 2H, CH=); ^{13}C NMR: δ = 20.3 (CH_2-CN), 21.0 (CH_3), 66.9 (CH_2-O), 67.3 (CH), 114.8 (CH=), 116.2 (CN), 122.0 (CH=), 129.9 (CH=), 158.0 (C), 170.1 (CO). GC retention times: 44.4 (*R*), 44.7 (*S*).

2-Cyano-1-(1-naphthoxymethyl)ethyl Acetate (2i): ^{1}H NMR: δ = 2.16 (s, 3H, CH_3), 2.98 (m, 2H, CH_2-CN), 4.29 (dd, 1H, CH_2-O, $^3J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 5.4 Hz), 4.35 (dd, 1H,

CH_2-O, $^3J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 4.8 Hz), 5.49 (m, 1H, CH), 6.81 (d, 1H, CH=, $^3J_{H,H}$ = 7.5 Hz), 7.37 (m, 1H, CH=), 7.50 (m, 3H, CH=), 7.82 (m, 1H, CH=), 8.19 (m, 1H, CH=); ^{15}C NMR: δ = 20.5 (CH_2-CN), 21.0 (CH_3), 67.2 (CH_2-O), 67.4 (CH), 105.3 (CH=), 116.2 (CN), 121.7 (CH=), 121.8 (CH=), 125.5 (CH=), 125.8 (CH=), 125.9 (CH=), 126.9 (CH=), 127.8 (CH=), 134.7 (C), 153.7 (C), 170.2 (CO). HPLC retention times: 23.9 (*S*), 42.5 (*R*).

2-Cyano-1-cyclohexylethyl Acetate (2j): The NMR data are in agreement with those previously reported.[7c] GC retention times: 38.9 (*R*), 39.4 (*S*).

2-Cyano-1-octylethyl Acetate (2k). The NMR data are in agreement with those previously reported.[7c] GC retention times: 41.6 (*S*), 42.1 (*R*).

General Procedure for the Kinetic Resolution of β-Hydroxy Nitriles: (*S*)-2-Cyano-1-phenylethyl Acetate [(*S*)-2a]

To a solution of (*rac*)-**1a** (29.4 mg, 0.2 mmol) and **3** (112 mg, 0.6 mmol) in dry toluene (2 mL) under argon (5 min of argon bubbling) was added the Novozym-435 (20 mg). The resulting reaction mixture was stirred at 60 °C for 24 hours. The enzyme was then filtered off and washed with toluene (3 × 5 mL), the solvent was evaporated and the product was analyzed. The product (*S*)-**2a** was obtained in 50% conversion and in >99% ee.[7a] The remaining 50% non-converted alcohol (*R*)-**1a** was analyzed and found to be >99% ee.

General Procedure for the DKR of β-Hydroxy Nitriles: (*S*)-2-Cyano-1-phenylethyl Acetate [(*S*)-2a]

In a typical experiment, ruthenium catalyst **8** (10.8 mg, 4 mol %) and Novozym-435 (20 mg) were placed in a Schlenk flask under argon. A solution of **1a** (34.8 mg, 0.2 mmol) and **3** (112 mg, 0.6 mmol) in dry toluene (2 mL) under argon (5 min of argon bubbling) was transferred to the ruthenium catalyst and the enzyme. The resulting reaction mixture was stirred at 100 °C for 36 hours. The enzyme was then filtered off and washed with toluene (3 × 5 mL), the solvent was evaporated and the residue was analyzed. The product (*S*)-**2a** was obtained in 74% yield and in 99% ee.

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