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Highly Efficient and Enantioselective Biotransformations of Racemic Azetidine-2-carbonitriles and Their Synthetic Applications

Dong-Hui Leng,[†] De-Xiang Wang,[†] Jie Pan,[†] Zhi-Tang Huang,[†] and Mei-Xiang Wang*[,†,‡]

[†]*Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China, and* [‡]*The Key Laboratory of Bioorganic Phosphorus Chemistry & Chemical Biology (Ministry of Education), Department of Chemistry, Tsinghua University, Beijing 100084, China*

mxwang@iccas.ac.cn

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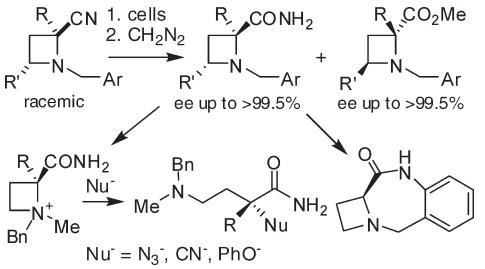

Catalyzed by the *Rhodococcus erythropolis* AJ270 whole cell catalyst in neutral aqueous buffer at 30 °C, a number of racemic 1-benzylazetidine-2-carbonitriles, *trans*-1-benzyl-4-methylazetidine-2-carbonitrile, and 1-benzyl-2-methylazetidine-2-carbonitrile and their amide substrates underwent efficient and enantioselective biotransformations to afford the corresponding azetidine-2-carboxylic acids and their amide derivatives in excellent yields with ee up to >99.5%. The overall excellent enantioselectivity of the biocatalytic reactions stemmed from a combined effect of a very active but virtually nonenantioselective nitrile hydratase and a high *R*-enantioselective amidase involved in microbial whole cells. The synthetic applications have been demonstrated by the nucleophilic ring-opening reactions of azetidiniums of the resulting chiral azetidine-2-carbox amide derivatives for the preparation of α,γ-diamino, α-phenoxy-γ-amino, and α-cyano-γ-amino carboxamides. The intramolecular CuI-catalyzed cross-coupling reaction for the synthesis of azetidine-fused 1,4-benzodiazepin-2-one derivative was also presented.

Introduction

Azetidine-2-carboxylic acids and their derivatives are important entities in organic chemistry.[1] As unique amino acids, for example, azetidine-2-carboxylic acid structures are found in natural products[1] such as mugineic acid, medicanine, and nocotianamine. Azetidine-2-carboxylic acid derivatives have been shown to have numerous potential applications in pharmaceutical and agrochemical fields.[1] Although it has not been fully explored, azetidine-2-carboxylic acid derivatives also provide valuable intermediates in organic synthesis.[2] Despite the importance, asymmetric synthesis of optically active azetidine-2-caroxylic acid derivatives has remained largely unexplored until recently. Most of the enantiopure azetidine-2-carboxylic acid derivatives, for instance, are obtained from multistep synthesis by using chiral starting materials and chiral auxiliaries,[3a−e] whereas the enantioenriched azetidine-2-carboxylic acid is obtained by

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optical resolution.[4] Using the lipase (Novozym 453) from *Candida antarctica* as a biocatalyst, Zwanenburg and coworkers have reported that racemic methyl *N*-alkylazetidine-2-carboxylates are resolved in an ammoniolysis reaction with good enantioselectivity in *tert*-butyl alcohol at 35 °C.[5] Esterase-catalyzed hydrolysis of racemic *N*-substituted azetidine-2-carboxylic acid esters has also been used to prepare optically active *N*-substituted azetidine-2-carboxylic acid compounds with moderate to good enantioselectivity.[6]

Biotransformations of nitriles,[7] either through a direct conversion from a nitrile to a carboxylic acid catalyzed by a nitrilase or through the nitrile hydratase-catalyzed hydration of a nitrile followed by the amide hydrolysis catalyzed by the amidase, have become the effective and environmentally benign methods for the production of carboxylic acids and their amide derivatives. One of the well-known examples is the industrial production of acrylamide from biocatalytic hydration of acrylonitrile.[8] Recent studies have demonstrated that biotransformations of nitriles complement the existing asymmetric chemical and enzymatic methods for the synthesis of chiral carboxylic acids and their derivatives.[9,10] One of the distinct features of enzymatic transformations of nitriles is the straightforward generation of enantiopure amides, valuable organo-nitrogen compounds in synthetic chemistry, in addition to the formation of enantiopure carboxylic acids. For example, we[9c] have shown that *Rhodococcus erythropolis* AJ270,[11] a nitrile hydratase/amidase-containing whole cell catalyst, is able to efficiently and enantioselectively transform a variety of racemic nitriles into highly enantiopure carboxylic acids and amides. Using the highly enantioselective nitrile biotransformation approach, many structurally diverse acids and amides that contain a three-membered ring such as cyclopropane,[12] epoxide,[13] and aziridine[14] have been synthesized. Our interests in small ring compounds[12−14] and in exploration of nitrile biotransformations in organic synthesis led us to undertake the current study. Herein, we report biotransformations of racemic azetidine-2-carbonitriles, a highly efficient method for the preparation of enantiopure azetidine-2-carboxylix acids and amides, and their applications in synthesis.

Results and Discussion

We initially examined the biotransformation of racemic 1-benzylazetidine-2-carbonitrile **1a**. To facilitate the isolation of product, acid **3a** was converted into its methyl ester with CH_2N_2 (Table 1). It was found that, catalyzed by *Rhodococcus erythropolis* AJ270 whole cell catalyst in neutral aqueous potassium phosphate buffer at 30 °C, hydrolysis of **1** proceeded very efficiently and enantioselectively. Within about 3.25 h, for example, enantiopure 1-benzylazetidien-2-carboxamide *S*-**2a** and methyl 1-benzylazetidien-2-carboxylate *R*-**4a** were obtained in good yield (entry 1, Table 1). To study the effect of the substituent of benzyl on the reaction, racemic nitrile analogues **1b**−**f** were prepared according to a literature precedure[3a] and subjected to biotransformations. As indicated by Table 1, irrespective of the electronic nature of the substituent on the benzyl, substrates **1b**−**e** tested underwent very rapid biotransformations to afford the corresponding amides *S*-**2b**−**e** and esters *R*-**4b**−**e** in high yields (entries 3−6, Table 1). Only when the substrate contains a 1-(2-bromobenzyl) group did the biotransformation of **1f** proceed very sluggishly. Excellent yields of *S*-**2f** and *R*-**3f** were achieved after 5 days of incubation of **1f** with microbial whole cell catalyst (entry 7, Table 1). It is noteworthy that all nitrile biotransformations produced highly enantiomerically enriched amide and acid products with an enantiomeric ratio E[15] being higher than 89, indicating excellent enantioselectivity of nitrile biotransformations. The biocatalytic reaction was also readily scaled up. This has been demonstrated by a gram scale preparation of enantiopure 1-benzylazetidien-2-carboxamide *S*-**2a** and methyl 1-benzylazetidien-2-carboxylate *R*-**4a** in good yield (entry 3, Table 1).

To understand the catalytic efficiency and stereochemistry of the nitrile hydratase and the amidase involved in *Rhodococcus erythropolis* AJ270, kinetic resolution of nitrile

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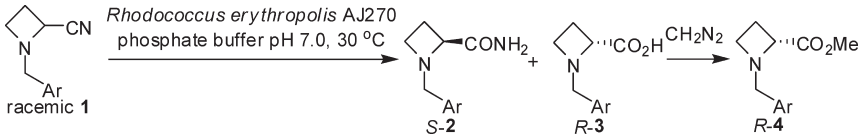
TABLE 1. Enantioselective Biotransformations of Racemic Azetidine-2-carbonitriles[a]



				S-**2**		*R*-**4**		
entry	**1**	Ar	time (h)	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[c]	E[d]
1	**1a**	C_6H_5	3.25	43	>99.5	41	>99.5	>200
2[e]	**1a**	C_6H_5	9.5	46	>99.5	49	>99.5	>200
3[f]	**1a**	C_6H_5	12.25	42	>99.5	40	>99.5	>200
4	**1b**	4-Me-C_6H_4	4.7	45	>99.5	39	>99.5	>200
5	**1c**	4-MeO-C_6H_4	3	45	>99.5	37	90.8	111
6	**1d**	4-Br-C_6H_4	4.25	43	>99.5	43	89.0	89
7	**1e**	3-Br-C_6H_4	4.75	42	>99.5	42	>99.5	>200
8	**1f**	2-Br-C_6H_4	5d	42	96.6	45	>99.5	>200

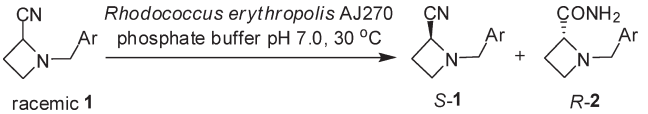
[a]Nitrile (1 mmol) was incubated with *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in potassium phosphate buffer (0.1 M, pH 7.0, 50 mL) at 30 °C. [b]Isolated yield. [c] Determined by chiral HPLC analysis. [d]Calculated following a literature method.[15] [e]Nitrile (2 mmol) was used. [f] Nitrile (13 mmol), cells (6 g wet weight), and buffer (150 mL) were used.

hydration and of amide hydrolysis was studied by controlling the reaction time. As summarized in Table 2, biocatalytic hydration of racemic nitriles **1a**, **1d**, and **1e** was extremely rapid, with ca. 50% conversion being achieved within 30 min. *S*-Nitrile and *R*-amide were obtained with very low ee values. This indicated that the nitrile hydratase involved in *Rhodococcus erythropolis* AJ270 is of very low *R*-enantioselectivity against azetidine-2-carbonitrile substrates. The outcomes are consistent with previous observations[9] that the nitrile hydratases are a type of highly active but less enantioselective enzyme against various nitrile substrates. These properties of the nitrile hydratase, such as having a broad substrate spectrum and possessing low or no enantioselectivity, are intrinsically determined by its enzyme structure in which there is a spacious pocket near the active site.[9,16] In other words, a pair of enantiomers of 1-arylmethylazetidine-2-carbonitriles are hardly differentiated by the nitrile hydratase, and almost identical biocatalytic hydration reactions were effected.

In contrast to the nitrile hydratase-catalyzed nitrile hydration reaction, amidase-catalyzed kinetic resolution exhibited excellent enantioselectivity. Biotransformation of racemic amides **2a**, **2e**, and **2f** afforded excellent yields of the corresponding amide *S*-**2** and ester *R*-**4** of high enantiopurity (Table 3). These results are also in agreement with the conclusion that the amidase within *Rhodococcus erythropolis* AJ270 microbial cell is highly enantioselective.[9,12−14] It can be concluded that the overall excellent enantioselectivity of the nitrile biotransformations summarized in Table 1 originates from the combined effect of a virtually nonenantioselective nitrile hydratase and a high *R*-enantioselective amidase, with the latter being the dominant one.

The structures of all products were established on the basis of spectroscopic data and microanalysis (see the Supporting Information). The absolute configuration of amide products was determined unambiguously by the single crystal X-ray diffraction analysis of enantiopure *S*-**2d** (see the Supporting Information), while the absolute configuration of the ester

TABLE 2. Biocatalytic Kinetic Resolution of Nitriles[a]



				S-**1**		*R*-**2**	
entry	**1**	Ar	time	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[c]
1	**1a**	C_6H_5	20 s	43	13.0	55	4.9
2	**1d**	4-Br-C_6H_4	3 min	57	2.6	42	6.4
3	**1e**	3-Br-C_6H_4	30 min	42	3.4	45	1.2

[a]Nitrile (1 mmol) was incubated with *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in potassium phosphate buffer (pH 7.0) at 30 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

products was obtained by comparing the optical rotation of *R*-**4b** ($[\alpha]^{25}_D$ +88 (*c* 0.5, $CHCl_3$)) with that of *S*-**4b** ($[\alpha]^{25}_D$ −84 (*c* 0.5, $CHCl_3$), which was obtained from the chemical transfromation of *S*-**2b** (Scheme 1).

Encouraged by the successful enantioselective biotransformations of 1-benzylazetidine-2-carbonitrile substrates, we attempted the hydrolysis of *trans*- and *cis*-1-benzyl-4-methylazetidine-2-carbonitriles.[17] Under the identical biocatalytic conditions, the racemic *trans*-1-benzyl-4-methylazetidine-2-carbonitrile (±)-**5** underwent efficient nitrile hydratase-catalyzed hydration reaction to afford amide (±)-**6**. Around 50% conversion, both nitrile recovered and amide product isolated were nearly racemic (Scheme 2), indicating again that the nitrile hydratase is almost nonenantioselective. As expected, the amidase involved in *Rhodococcus erythropolis* AJ270 catalyzed enantioselective hydrolysis of racemic amide (±)-**6** to produce very good yields of highly enantioenriched (−)-1-benzyl-4-methylazetidine-2-carboxamide (−)-**6** and (+)-1-benzyl-4-methylazetidine-2-carboxylic acid. The latter was converted into the ester

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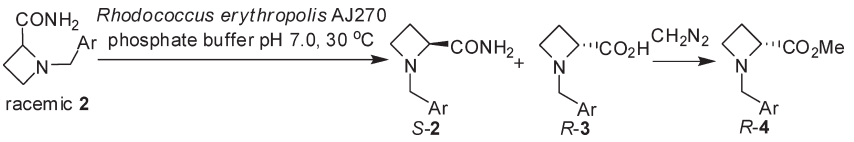
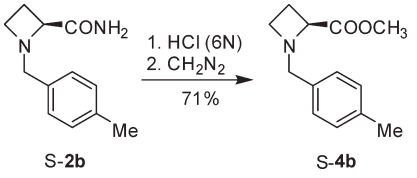
TABLE 3. Biocatalytic Kinetic Resolution of Amides[a]



				S-2		*R*-4		
entry	**2**	Ar	time	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[c]	E[d]
1	**2a**	C_6H_5	3.7 h	49	>99.5	40	>99.5	>200
2	**2e**	3-Br-C_6H_4	6.3 h	47	93.8	49	>99.5	>200
3	**2f**	2-Br-C_6H_4	5 d	46	96.6	49	>99.5	>200

[a]Amide (1 mmol) was incubated with *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in potassium phosphate buffer (pH 7.0) at 30 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Calculated following a literature method.[15]

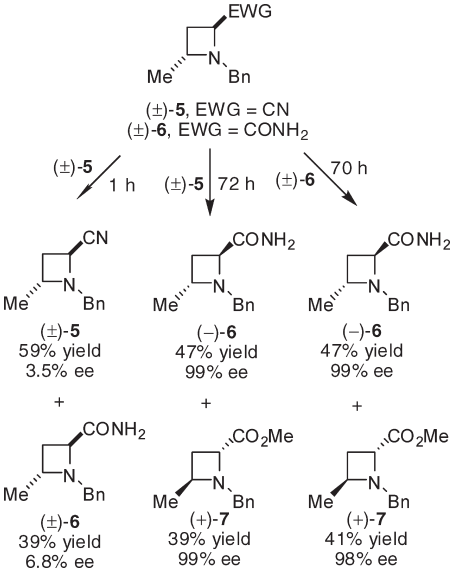
SCHEME 1. Chemical Transformation of Amide *S*-2b into Ester *S*-4b



product (+)-**7**. The highly enantiopure amide (−)-**6** and ester (+)-**7** were prepared similarly from the biotransformations of racemic nitrile (±)-**5** (Scheme 2). In contrast to *trans*-1-benzyl-4-methylazetidine-2-carbonitrile (±)-**5**, *cis*-1-benzyl-4-methylazetidine-2-carbonitrile was not a good substrate at all for the nitrile hydratase within *Rhodococcus erythropolis* AJ270. For example, the starting nitrile was recovered almost quantitatively after 7 days of interaction with microbial cells. The dramatic difference in the nitrile hydration reaction between *trans*- and *cis*-1-benzyl-4-methylazatidine-2-carbonitriles suggested that the pocket of active site of the nitrile hydratase is also size- or shape-selective against nitrile substrate. It is capable of recognizing and transforming *trans*-1-benzyl-4-methylazetidine-2-carbonitrile rather than the cis-isomer.

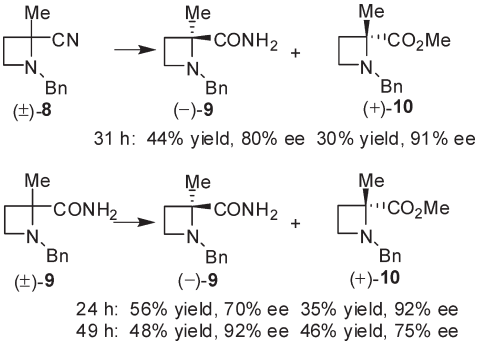
When a methyl group was introduced into the 2-position of 1-benzylazetidine-2-carbonitirle, the resulting quaternary-carbon-containing nitrile (±)-**8** was also accepted by the biocatalyst as a fairly good substrate. Interaction of (±)-**8** with *Rhodococcus erythropolis* AJ270 for 31 h led to the isolation of enantioenriched (−)-1-benzyl-2-methylazatidine-2-carboxamide (−)-**9** (ee 80%) and methyl (+)-1-benzyl-2-methylazetidine-2-carboxylate (+)-**10** (ee 91%) in 44% and 30% yields, respectively. Optically inactive starting nitrile was also recovered in 16% yield (Scheme 3). To prepare highly enantiopure (−)-1-benzyl-2-methylazatidine-2-carboxamide (−)-**9** and methyl (+)-1-benzyl-2-methylazetidine-2-carboxylate (+)-**10**, kinetic resolution of racemic amide (±)-**9** was carried out. By controlling the conversion, both (−)-**9** and (+)-**10** were obtained with ee up to 92% (Scheme 3). It is noteworthy that the amidase-catalyzed hydrolysis of racemic amides (±)-**6** and (±)-**9** proceeded much slower than the reaction of racemic amide (±)-**2a**. This implies that the amidase is very sensitive to the steric effect of the substrate. One more methyl group introduced into the azetidine ring increased the bulkiness of the substrate, and led therefore to a diminished reaction rate.

SCHEME 2. Enantioselective Biotransformations of Racemic *trans*-1-Benzyl-4-methylazetidine-2-carbonitrile 5 and Amide 6[a]



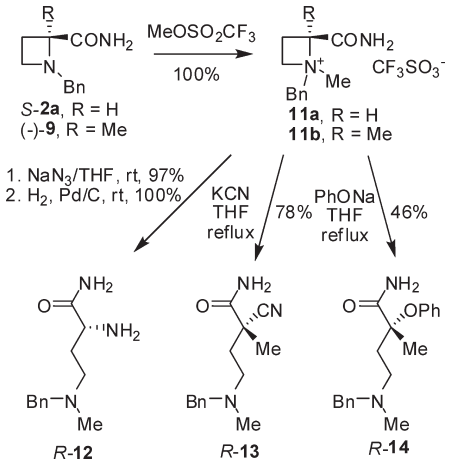
[a]Substrate (2 mmol) was incubated with Rhodococcus erythropolis AJ270 cells (2 g wet weight) in potassium phosphate buffer (pH 7.0) at 30 °C. The acid product was converted into methyl ester with CH_2N_2.

SCHEME 3. Enantioselective Biotransformations of Racemic 1-Benzyl-2-methylazetidine-2-carbonitrile 8 and Amide 9[a]

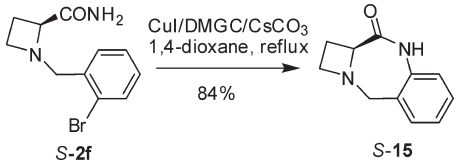


[a]Substrate (2 mmol) was incubated with Rhodococcus erythropolis AJ270 cells (2 g wet weight) in potassium phosphate buffer (pH 7.0) at 30 °C. The acid product was converted into methyl ester with CH_2N_2. For the biotransformation of (±)-8, 16% of starting nitrile (ee 0%) was recovered.

SCHEME 4. Nucleophilic Ring-Opening Reactions of Azetidinium Salts 11



SCHEME 5. Synthesis of *S*-1,2,8,10a-Hetrahydroazeto[1,2-*a*]benzo[*e*][1,4]diazepin-10(4*H*)-one 15



Enantiopure azetidine-2-carboxylic acids and their derivatives obtained from nitrile biotransformations are useful chiral intermediates in organic synthesis. To explore their synthetic applications, we studied the ring-opening reaction of 1-benzylazetidine-2-carboxamide *S*-**2a** and 1-benzyl-2-methylazetidine-2-carboxamide (−)-**9**. Being different from aziridine-2-carboxylic acid derivatives which undergo ring-opening reactions readily, azetidine-2-carboxamides are stable. To increase the reactivity of ring-opening reactions, azetidine-2-carboxamides were first converted into azetidinium species **11** simply by treatment with methyl trifluoromethanesulfonate. The azetidinium intermediates **11** are reactive toward nucleophiles under mild conditions. For example, sodium azide attacked regioselectively at the 2-position of **11a** in THF at room temperature to afford the ring-opening reaction product in excellent yield. The subsequent catalytic hydrogenation of the azido group led to the quantitative formation of α,γ-diamino butyramide derivative *R*-**12**. In refluxing THF, azetidinium **11b** underwent similar regionselective nucleophilic ring-opening reactions with potassium cyanide and sodium phenoxide, respectively, to yield quaternary carbon-containing polyfunctionalized carboxamides *R*-**13** and *R*-**14** (Scheme 4). It is worth noting that all reactions gave configuration inversion products without racemerization. Further synthetic application of chiral azetidine-2-carboxamides was demonstrated by the preparation of azetidine-fused heterocyclic product. *S*-1,2,8,10a-Hetrahydroazeto[1,2-*a*]benzo[*e*][1,4]diazepin-10-(4*H*)-one **15** (94.1% ee), a unique 1,4-benzodiazepin-2-one analogue, was obtained in good yield from intramolecular cross-coupling reaction of *S*-**2f** (ee 92.6%) catalyzed by CuI/*N*,*N*-dimethylglycine (DMGC) under basic conditions (Scheme 5).

Conclusion

In summary, we have developed an efficient nitrile biotransformation method for the synthesis of highly enantiopure azetidine-2-carboxylic acids and amide derivatives. The overall excellent enantioselectivity of the biocatalytic reactions stemmed from an active but virtually *non*enantioselective nitrile hydratase and a high *R*-enantioselective amidase involved in *Rhodococcus erythropolis* AJ270 whole cell catalyst. We have shown that the resulting azetidine-2-carboxylic acid derivatives are useful chiral compounds for the synthesis of polyfunctionalized organic compounds such as α,γ-diamino, α-phenoxy-γ-amino, and α-cyano-γ-amino carboxamides via the regioselective nucleophilic ring-opening reactions of azetidinium intermediates. Synthetic application was also demonstrated by the preparation of an azetidine-fused 1,4-benzodiazepin-2-one derivative from CuI-catalyzed intramolecular cross-coupling reaction. Further study of enantioselective biotransformations of small heterocyclic nitriles and their synthetic applications is actively pursued in this laboratory.

Experimental Section

General Procedure for the Biotransformation of Nitriles and Amides. To an Erlenmeyer flask (150 mL) with a screw cap were added *Rhodococcus erythropolis* AJ270 cells[11] (2 g wet weight) and potassium phosphate buffer (0.1 M, pH 7.0, 50 mL), and the resting cells were activated at 30 °C for 0.5 h with orbital shaking. Racemic nitriles or amide (see Tables 1−3) were added in one portion to the flask, and the mixture was incubated at 30 °C, using an orbital shaker (200 rpm). The reaction, monitored by TLC and HPLC, was quenched after a specified period of time (see Tables 1−3) by removing the biomass through a Celite pad filtration. The resulting aqueous solution was extracted with ethyl acetate. After drying (Na_2SO_4) and removing the solvent under a vacuum, the residue of the organic phase was chromatographed on a silica gel column with a mixture of petroleum ether and ethyl acetate as the mobile phase to give pure amide product **2** and recovered nitrile **1**. The aqueous phase was freeze-dried (−50 to −60 °C), and the residue was treated with CH_2N_2 in ether below −15 °C. When finished, the reaction was quenched by some water and then extracted with ethyl acetate. After drying (Na_2SO_4) and removing the solvent under a vacuum, the pure methyl ester **4** was left. In a multigram scale reaction, racemic nitrile **1a** (2.24 g, 13 mmol) was converted into *S*-**2a** and *R*-**4a**.

(*S*)-(−)-1-Benzylazetidine-2-carboxamide (*S*-2a): 1.03 g, 42%; white solid; mp 93.0−94.0 °C; IR (KBr) ν 3379, 3265, 3158, 1682, 1652 cm^{-1}; $[\alpha]^{25}_D$ −104 (*c* 0.5, $CHCl_3$); ee >99.5% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.25−7.35 (m, 5H), 7.00 (s, 1H), 5.43 (s, 1H), 3.72 (d, J = 12.7 Hz, 1H), 3.68 (t, J = 8.6 Hz, 1H), 3.57 (d, J = 12.8 Hz, 1H), 3.37 (m, 1H), 3.01 (q, J = 16.3 Hz, 1H), 2.37−2.47 (m, 1H), 2.11−2.23 (m, 1H); ^{13}C NMR(75 MHz, $CDCl_3$) δ 176.2, 137.3, 128.6, 128.6, 127.4, 66.1, 62.3, 50.8, 23.0; MS (ESI) *m*/*z* (%) 191 $[M + H]^+$. Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found: C, 69.10; H, 7.45; N, 14.55.

(*R*)-(+)-Methyl 1-benzylazetidine-2-carboxylate (*R*-4a): 1.07 g, 40%; oil; IR (KBr) ν 1743 cm^{-1}; $[\alpha]^{25}_D$ +96 (*c* 0.5, $CHCl_3$), +118 (*c* 1.0 CH_2Cl_2) [lit.[3a] +125 (*c* 1.0 CH_2Cl_2)]; ee >99.5% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.23−7.33 (m, 5H), 3.80 (d, J = 12.6 Hz, 1H), 3.74 (t, J = 8.4 Hz, 1H), 3.64 (s, 3H), 3.58 (d, J = 12.6 Hz, 1H), 3.29−3.35 (m, 1H), 2.91−2.98 (m, 1H), 2.31−2.43 (m, 1H), 2.17−2.25 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1,137.0,129.0, 128.3, 127.2, 64.3, 62.3, 51.7, 50.8, 21.6; MS (ESI) *m*/*z* (%) 206 $[M + H]^+$. Anal. Calcd for

$C_{11}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.46; H, 7.58; N, 6.85.

General Procedure for the Formation of Azetidinium Trifluoromethanesulfonate 11. Methyl trifluoromethanesulfonate (0.45 mL, 4 mmol) was added dropwise to a solution of chiral azetidine (2 mmol) in DCM (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. After the solvent was evaporated, the resulting residue was washed with a small amount of dry diethyl ether and dried under vacuum to afford pure azetidinium trifluoromethanesulfonate **11**.

General Procedure for the Ring-Opening Reactions of Azetidinium Salts. The nucleophilic reagent (5 mmol) was added to a solution of azetidinium trifluoromethanesulfonate **11** (1 mmol) in THF (5 mL). The suspension was stirred at room temperature for 12 h or refluxed overnight. Water (5 mL) was added and the resulting aqueous solution was extracted with ethyl acetate. After the solution was dried (Na_2SO_4) and the solvent was removed under vacuum, the residue of the organic phase was chromatographed on a silica gel column, using a mixture of petroleum ether and ethyl acetate (1:1) as the mobile phase, to give pure product **12**−**14**.

Procedure for the Synthesis of (*S*)-1,2,8,10a-Hetrahydroazeto-[1,2-*a*]benzo[*e*][1,4]diazepin-10(4*H*)-one 15. Under argon protection, a mixture of substrate *S*-**2f** (1 mmol), CuI (0.4 mmol, 76 mg), *N*,*N*-dimethylglycine hydrochloride (0.8 mmol, 112 mg), Cs_2CO_3 (2 mmol, 650 mg), and dry 1,4-dioxane (34 mL) was refluxed for 3 h. After cooling, ethyl acetate (100 mL) was added and the resulting mixture was filtrated through a short silica gel (100−200 mesh) pad. The filtrate was concentrated and the residue was filtered with a silica gel column (100−200 mesh) and washed by ethyl acetate to give a crude product of **15**. The second silica gel (200−300 mesh) column chromatography eluted with a mixture of petroleum ether and ethyl acetate (1:1) to give pure product **15** (152 mg, 81%) as white solids: mp 156.0−157.0 °C; IR (KBr) ν 3220, 1674, 1635 cm^{-1}; $[\alpha]^{25}_D$ +28 (*c* 0.5, $CHCl_3$); ee 94.1% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.27−7.32 (m, 2H), 7.16 (t, J = 7.3 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 4.06 (dd, J = 2.6 Hz, 7.8 Hz, 1H), 3.74 (d, J = 10.9 Hz, 1H), 3.67 (d, J = 10.9 Hz, 1H), 3.44−3.52 (m, 2H), 2.61−2.67 (m, 1H), 2.36−2.46 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 136.8, 130.3, 129.9, 128.7, 125.7, 121.5, 64.2, 56.7, 54.7, 30.8, 19.5; MS (ESI) *m*/*z* (%) 189 $[M + H]^+$. Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.86; H, 6.41; N, 15.02.

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Supporting Information Available: Characterization of products, ^1H and ^{13}C NMR spectra of products, and X-ray structure of *S*-**2d** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.