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Nitrile Biotransformations for the Efficient Synthesis of Highly Enantiopure 1-Arylaziridine-2-carboxylic Acid Derivatives and Their Stereoselective Ring-Opening Reactions

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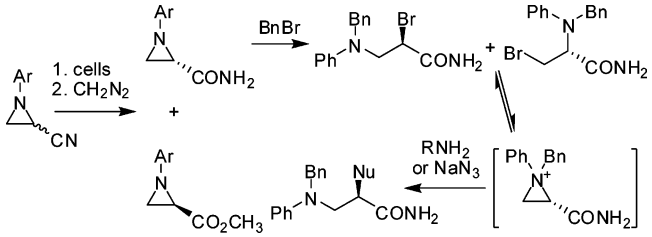

Catalyzed by the *Rhodococcus erythropolis* AJ270 whole cell catalyst under very mild conditions, biotransformations of racemic 1-arylaziridine-2-carbonitriles proceeded efficiently and enantioselectively to produce highly enantiopure *S*-1-arylaziridine-2-carboxamides and *R*-1-arylaziridine-2-carboxylic acids in excellent yields. Although the nitrile hydratase exhibits no selectivity against all nitrile substrates, the amidase is highly *R*-enantioselective towards 1-arylaziridine-2-carboxamides. When treated with benzyl bromide, 1-phenylaziridine-2*S*-carboxamide underwent a highly regioselective and enantiospecific ring-opening reaction to afford an almost quantitative yield of *R*-β-[(benzyl)phenylamino]-α-bromopropanamide (C-2 attack) and *R*-α-[(benzyl)phenylamino]-β-bromopropanamide (C-3 attack) in a 10.5:1 ratio. Further treatment of the resulting ring-opening products with an N-nucleophilic reagent such as amine and azide led to, through most probably the aziridinium intermediate, the formation of *S*-α-substituted-β-[(benzyl)-phenylamino]propanamides in good chemical yields with high enantiomeric purity.

Introduction

There is a rapid increasing interest[1,2] in aziridine derivatives because of their intriguing and unique chemical and biological properties. Among aziridine compounds, chiral aziridine-2-carboxylic acid derivatives, a type of special amino acid derivatives, are of special importance owing to their occurrence in natural products and in synthetic pharmaceuticals and to their versatility in the preparation of diverse chiral molecules.[1−3] In contrast to oxirane-2-carboxylic acid derivatives,[4] the synthesis of optically active aziridine-2-carboxylates still remains challenging to synthetic chemists. For example, most chiral aziridine-2-carboxylates were prepared using either chiral starting materials[1b,3b,5] or chiral auxiliaries,[1b,3b,6] and most of them are generally time consuming or not cost effective. Although catalytic asymmetric syntheses have been reported,[3b,6f,7] they

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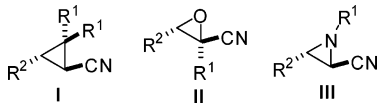
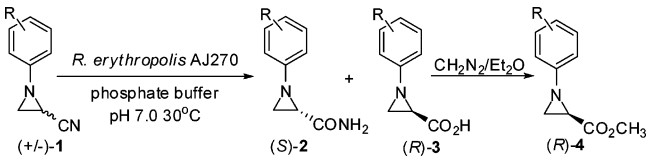
are limited to a narrow substrate spectrum. Recently, the lipase-mediated kinetic resolution of racemic 1-arylaziridine-2-carboxylates has been shown to give in most cases disappointingly low chemical yield and enantioselectivity.[8]

Biotransformations of nitriles, 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.[9] One of the well-known examples is the industrial production of acrylamide from biocatalytic hydration of acrylonitrile.[10] 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.[11,12] The distinct features of enzymatic transformations of nitriles are 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 have shown that *Rhodococcus erythropolis* AJ270,[13] a nitrile hydratase/amidase-containing whole cell catalyst, is able to efficiently and enantioselectively

CHART 1. Nitriles Bearing a Three-Membered Ring



SCHEME 1. Biotransformations of Racemic 1-Arylaziridine-2-carbonitriles 1



transform a variety of racemic nitriles bearing an α-[14] or a β-stereocenter[15] and prochiral dinitriles[16] into highly enantiopure carboxylic acids and amides. More significantly, biotransformations of nitriles bearing a three-membered ring such as cyclopropanecarbonitriles **I**[17] and oxiranecarbonitriles **II**[4,18] (Chart 1) proceeded in a highly predictable manner in terms of reaction efficiency and enantioselectivity based on the substituents and configurations of the substrates. Encouraged by our previous study, we envisioned that aziridine-2-carbonitriles **III** (Chart 1), which have steric features similar to those of cyclopropanecarbonitriles **I** and oxiranecarbonitriles **II**, might be the suitable substrates to the microbial cell catalyst. Herein, we report the highly efficient biotransformations of racemic 1-arylaziridine-2-carbonitriles for the synthesis of enantiopure 1-arylaziridine-2-carboxylic acids and their derivatives. The stereoselective aziridine ring-opening reactions in the synthesis of chiral α,β-diamino acid derivatives will also be discussed.

Results and Discussion

We first tested the biotransformation of racemic 1-phenylaziridine-2-carbonitrile **1a** (Scheme 1). When incubated with *Rhodococcus erythropolis* AJ270 microbial cells in phosphate buffer with pH 7.0 at 30 °C for less than 1 h, nitrile **1a** (2 mmol) underwent efficient hydrolysis to afford excellent yields of *S*-1-phenylaziridine-2-carboxamide **2a** and methyl *R*-1-phenylaziri-

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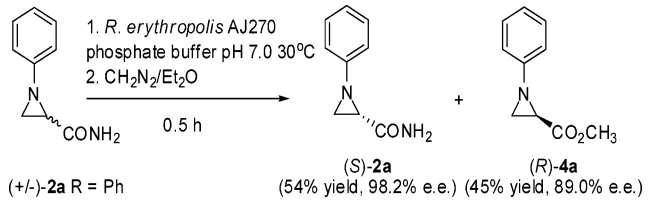
TABLE 1. Biotransformations of Racemic 1-Arylaziridine-2-carbonitriles 1

entry	R	time[a]	2	yield (%)[b]	ee (%)[c]	4	yield (%)[b]	ee (%)[c]	E[d]
1	H	0.92 h	**2a**	48	96.2	**4a**	47	91.0	83
2	4-F	0.67 h	**2b**	48	>99.5	**4b**	50	93.8	>200
3	4-Cl	0.5 h	**2c**	46	95.4	**4c**	49	87.0	53
4	4-Br	5 h	**2d**	25	>99.5	**4d**	74	67.0	–
5[e]	4-Br	1.25 h	**2d**	48	89.0	**4d**	45	93.0	82
6[f]	4-MeO	0.67 h	**2e**	28	96.0	**4e**	22	>99.5	–
7	4-MeO	3 h	**2e**	47	>99.5	**4e**	46	96.0	>200
8[e]	4-MeO	1.75 h	**2e**	48	>99.5	**4e**	47	96.0	>200
9	4-Me	1.25 h	**2f**	50	>99.5	**4f**	50	>99.5	>200
10	3-Me	5 h	**2g**	45	96.7	**4g**	50	90.4	79
11	2-Me	4 d	**2h**	48	0	**4h**	47	0	–
12[g]	H	2 h	**2a**	45	>99.5	**4a**	47	85.2	90

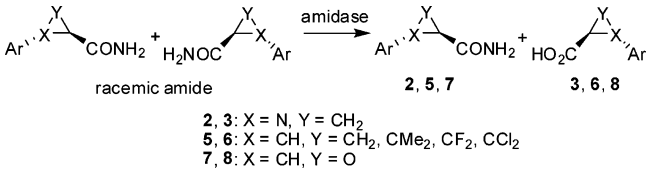
[a] Reaction time was optimized to the completion of nitrile conversion and roughly 50% conversion of the amide using HPLC analysis. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Calculated according to ref 20. [e] Acetone (4 mL) was used as a cosolvent. [f] Optically inactive nitrile **1h** (49% yield) was recovered. [g] Racemic nitrile **1a** (15 mmol) was incubated with 6 g wet weight of microbial cells.

dine-2-carboxylate **4a**,[6f] the latter being obtained from the esterification of *R*-1-phenylaziridine-2-carboxylic acid **3a**, with 96.2% and 91.0% enantiomeric excesses, respectively (entry 1, Table 1). The absolute configuration of product *R*-**4a** was determined by the comparison of its optical rotation with that of the authentic sample.[6f] Encouraged by this result, a number of racemic 1-arylaziridine-2-carbonitriles **1b**−**h** were prepared[19] and subjected to the biotransformations under the identical conditions (Scheme 1). It was found that all nitriles were rapidly hydrated to amides under the action of the nitrile hydratase within the cells, and the hydrolysis of the resulting amides catalyzed by the amidase was also efficient in most cases. As summarized in Table 1, almost all substrates reached 50% amide transformation into the carboxylic acids within 5 h except racemic 1-(2-methylphenyl)aziridine-2-carbonitrile **1h** which took 4 days to yield the same amount of amide **2h** and acid **3h** (entry 11, Table 1). For substrates such as **1d** and **1e** that did not dissolve or disperse in culture suspension, addition of acetone as a cosolvent had a beneficial effect to accelerate their conversions (entries 4, 5, 7, and 8, Table 1). Biotransformations of 1-arylaziridine-2-carbonitriles proceeded with excellent enantioselectivity, and the enantiomeric ratio E[20] was as high as >200 (Table 1). For example, almost all nitriles **1a**−**g** gave high enantiomeric excess values of the amide and acid products irrespective of the electronic nature of the substituent on the benzene ring. However, the substitution pattern led to a drastic effect on the enantioselectivity of the reaction. Although the biotransformations of 1-(*p*-methylphenyl)aziridine-2-carbonitrile **1f** and 1-(*m*-methylphenyl)aziridine-2-carbonitrile **1g** yielded excellent enantiocontrol, only optically inactive amide and acid products were produced from *o*-methylphenyl-substituted aziridine-2-carbonitrile analogue **1h** (entries 9−11, Table 1). To understand the stereochemistry and enantioselectivity of the enzymes involved in catalysis, the microbial transformation of racemic **1e** was quenched when half of the nitrile was transformed. The isolation of optically inactive nitrile **1h** and the enantiopure *S*-amide **2h** (ee 96.0%) and ester *R*-**4h** (ee > 99.5%) (entry 6, Table 1) indicated a nonselective nitrile

SCHEME 2. Biocatalytic Resolution of Racemic Amide 2a



SCHEME 3. Enantioselectivity of Amidase in the Hydrolysis of Amides Bearing a Three-Membered Ring



hydratase and a highly *R*-enantioselective amidase in *Rhodococcus erythropolis* AJ270 cells. The excellent *R*-enantioselectivity of the amidase was further demonstrated by the kinetic resolution of racemic 1-phenylaziridine-2-carboxamide **2a**, which produced *S*-**2a** and *R*-**3a** with good enantiomeric purity (Scheme 2). It is noteworthy that nitrile biotransformations can be readily used to prepare highly enantiopure 1-phenylaziridine-2-carboxylic acid derivatives in a gram scale (entry 12, Table 1).

The outcomes of the current study are consistent with previous observations that nitrile hydratases are a type of highly active and less selective enzyme against a wide variety of nitrile substrates.[9] 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.[17,18,21] In other words, a pair of enantiomers of 1-arylaziridine-2-carbonitriles, analogous to trans-configured 2-arylcyclopropanecarbonitriles[17] and 2-aryloxiranecarbonitriles,[4,18] are not recognized or differentiated by the nitrile hydratase, and almost identical biocatalytic hydration reactions were therefore effected.

The formation of highly enantiopure 1-arylaziridine-2*R*-carboxylic acids from the biotransformations of almost all racemic nitrile and amide substrates indicated again that the amidase involved in *Rhodococcus erythropolis* AJ270 is an enantioselective enzyme.[11c] Very interestingly, examination of the stereochemistry of the amide and acid products from the biotransformations of the corresponding nitriles and amides containing a three-membered ring including aziridine, cyclopropane,[17] and oxirane[4,18] revealed that the amidase is able to recognize all carboxamides with a trans-arylated three-membered ring in the same steric sense. In other words, irrespective of the nature of the ring, all three-membered ring-substituted carboxamides can be kinetically resolved into the optically active amide and acid by the amidase following the same chiral selection model (Scheme 3). It is worth noting that the aryl group on the nitrogen of the aziridine is most likely to adopt a trans configuration relative to the amido group,[6f] though the pyramidal inversion might take place on aziridine nitrogen.[22] The almost identical chiral recognition of amidase toward 1-arylaziridine-2-carboxamides and other three-membered ring

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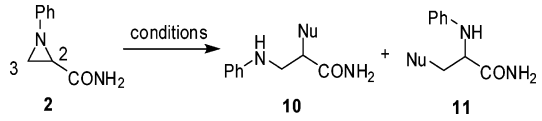
TABLE 2. Ring-Opening Reactions of Racemic 1-Phenylaziridine-2-carboxamide



2 10 11

entry	conditions	Nu	yield of **10** + **11** (%)[a]	**10**/**11**[b]
1	$BnNH_2/Cu(OTf)_2/CH_3CN$/rt	BnNH	−	−
2	$BnNH_2/Cu(OAc)_2/CH_3CN$/reflux	BnNH	−	−
3	$BnNH_2/Ti(O^iPr)_4/CH_3CN$/reflux	BnNH	−	−
4	$NaN_3/CF_3CO_2H/CH_3CN$/rt	N_3	trace	nd[c]
5	$NaN_3/Cu(OAc)_2/CH_3CN$/rt	N_3	−	−
6	$NaN_3/Cu(ClO_4)_2/CH_3CN/H_2O$/reflux	N_3	34	3.1:1
7	$NaN_3/BF_3{\cdot}OEt_2/CH_3CN$/reflux	N_3	76	1:1
8	$TMSN_3/Cu(ClO_4)_2/CH_3CN/H_2O$/reflux	N_3	89	3.1:1
9	$TMSN_3/Cu(CH_3CN)_4PF_6/CH_3CN$/reflux	N_3	90	3.1:1

[a] Isolated yield. [b] Determined by ^1H NMR. [c] Not determined.

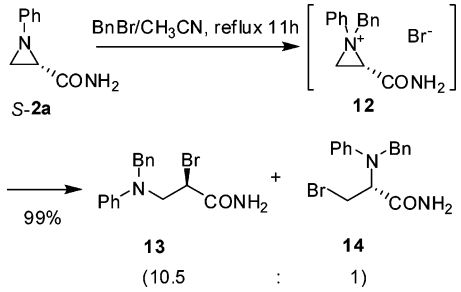
analogues fits well with the proposal[17,18] that the amidase in *Rhodococcus erythropolis* AJ270 might comprise a deeply buried and highly steric demanding active site. The hypothetic model can also be used to explain the huge difference in reaction efficiency and enantioselectivity between racemic 1-(2-methylphenyl)aziridine-2-carboxamide **2h** and other amides **2a**−**g**. Compared with the amides **2a**−**g** having a para or a meta substituent on the benzene ring, introduction of a substituent such as methyl on the ortho position of the benzene ring increased the steric bulkiness of the substrate. This steric effect might inhibit the effective interaction of **2h** with the highly sterically sensitive amidase, leading to a very sluggish and nonenantioselective biotransformation.

As a unique type of intermediates in organic synthesis, the ring-opening reactions of aziridines have attracted much attention.[1−3] However, the studies on the reactions of aziridine-2-carboxylic acids and their derivatives are very limited.[3b] Having had a simple and straightforward biotransformation approach to highly enantiopure 1-arylaziridine-2-carboxylates and carboxamides, we started to explore their ring-opening reactions with a number of N-nucleophiles to synthesize α,*β*-diamino acids and derivatives.

Initially, we examined the reaction of racemic 1-phenylaziridine-2-carboxamide with benzylamine. No ring-opening products were observed, however, even in the presence of a Lewis acid catalyst (entries 1−3, Table 2). Sodium azide was then tested as a nucleophile. Only in the presence of $Cu(ClO_4)_2$ or $BF_3{\cdot}OEt_2$ as a catalyst did azide attack the aziridine to give ring-opening products in moderate yield (entries 4−7, Table 2). The chemical yield was then improved to 90% when $TMSN_3$ was employed instead of NaN_3 (entries 8 and 9, Table 2). Unfortunately, the ring-opening reaction did not yield satisfactory regioselectivity, forming α-azido-*β*-phenylaminopropanamide (C-2 attack product) **10** and α-phenylamino-*β*-azidopropanamide (C-3 attack product) **11** in a ratio of 1:1 to 3:1 (entries 6−9, Table 2).

We then envisioned that a large activation moiety on the aziridine ring while using a larger nucleophile would improve the regioselectivity of the ring-opening reaction of 1-phenylaziridine-2-carboxamide. To test our hypothesis, benzyl bromide[23] was chosen to react with **2**. To our delight, the reaction between enantiopure 1-phenylaziridine-2*S*-carboxamide **2a** and

SCHEME 4. Highly Regioselective and Enantiospecific Ring-Opening Reactions of *S*-2a by Benzyl Bromide



benzyl bromide proceeded efficiently in refluxing acetonitrile to give excellent yield of the ring-opening products. More importantly, the regioselectivity of the reaction improved significantly, with the ratio of α-bromo-*β*-[(benzyl)phenylamino]-propanamide **13** to α-[(benzyl)phenylamino]-*β*-bromopropanamide **14** being as high as 10.5:1 (Scheme 4). Chiral HPLC analysis showed that each of the products **13** and **14** was enantiomerically pure, indicating an enantiospecific ring-opening reaction. The ring-opening reaction was most likely to proceed through an aziridinium intermediate **12** (Scheme 4).[23,24]

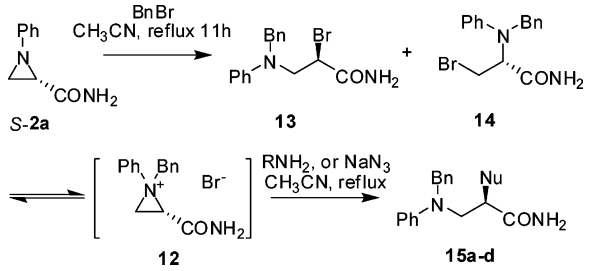
Having established a highly stereoselective ring-opening reaction, we then attempted the synthesis of chiral vicinal diamine compounds, very useful chiral intermediates in both medicinal chemistry and asymmetric synthesis. After completion of the ring-opening reaction of *S*-**2a** by benzyl bromide, the reaction mixture, without isolation of **13** and **14**, was treated directly with an N-nucleophile such as benzylamine, *N*-methyl-*N*-benzylamine, allylamine, and sodium azide. In all cases, α-substituted *β*-[(benzyl)phenylamino]propanamides **15a**−**d** were obtained in good yield. It should be pointed out that no desired products **15a**−**d** were produced if the conversion of *S*-**2a** into **13** and **14** was not effected prior to the addition of a nucleophile. The enantiomeric excess values of the products, however, varied from 78% to 95% depending on the nucleophile

(22) For pyramidal inversion of the aziridine ring, see: March, J. *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons, Inc.: New York, 1992; pp 98−99 and references therein.

(23) Very recently, benzyl bromide has also been used to open the 2-alkanoyloxymethyl-1-arylmentylaziridine ring. (a) D'hooghe, M.; Van Speybroeck, V.; Waroquier, M.; De Kimpe, N. *Chem. Commun.* **2006**, 1554. (b) D'hooghe, M.; De Kimpe, N. *Synlett* **2006**, 2089.

(24) The aziridinium intermediate was very recently proposed and utilized in the synthesis of enantiopure *β*-amino and α,*β*-diamino esters from the reaction of *N*,*N*-dibenzyl-*O*-methylsulfonyl serine methyl ester with nucleophilic reagents. Couturier, C.; Blanchet, J.; Schlama, T.; Zhu, J. *Org. Lett.* **2006**, *8*, 2183.

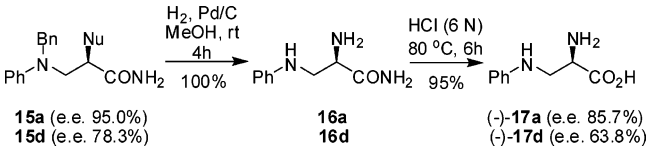
TABLE 3. Synthesis of Optically Active α,β-Diamino Carboxamides via the Benzyl Bromide Mediated Ring-Opening Reactions of 1-Phenylaziridine-2*S*-carboxamide 2a



entry	conditions	**15** (%)[a]	er (%)[b]
1	$PhCH_2NH_2$, 12 h	**15a** (87)	97.5:2.5
2	$PhCH_2NHMe$, 12 h	**15b** (89)	95.6:4.4
3	$CH_2{=}CHCH_2NH_2$, 24 h	**15c** (83)	92.0:8.0
4	NaN_3, 48 h	**15d** (78)	89.2:10.8

[a] Isolated yield. [b] Determined by chiral HPLC analysis.

SCHEME 5. Conversion of 15 into Optically Active 2*R*-Amino-3-(phenylamino)propanoic Acid 17



employed (Table 3). Most surprisingly, by comparison of the stereochemistry of aziridine *S*-**2a**, the eutomer of all products **15** had the opposite configuration at the C-2 position, which was determined by chemical conversion of **15** into the known 2*R*-amino-3-(phenylamino)propanoic acid **17**[25] (Scheme 5). This suggested that the reaction did not proceed through S_N2 nucleophilic replacement of the 2-bromo substituent of **13**. If the nucleophile attacked at C-2 of **13**, configuration inversion would occur to yield 2*S*-amino-3-(phenylamino)propanoic acid, a product retaining the absolute configuration of starting aziridine *S*-**2a**. The reaction between a nucleophile and **13** and **14** proceeded mainly via an aziridinium intermediate **12** which was generated in situ from the neighboring amino participation.[24] Observation of partial racemization of products **15** was most probably due to the competitive direct S_N2 substitution reaction pathway taking place on **13**. This competitive reaction route became more noticeable when a sterically less-hindered nucleophile such as allylamine or sodium azide was applied, which was exemplified by the isolation of less enantiopure products **15c** and **15d** (Table 3).

Conclusion

In summary, we have demonstrated that biotransformations of racemic 1-arylaziridine-2-carbonitriles, catalyzed by the *Rhodococcus erythropolis* AJ270 whole cell catalyst under very mild conditions, lead to an efficient synthesis of highly enantiopure *S*-1-arylaziridine-2-carboxamides and *R*-1-arylaziridine-2-carboxylic acids. Although the nitrile hydratase exhibits no selectivity against all nitrile substrates, the amidase is highly *R*-enantioselective toward 1-arylaziridine-2-carboxamides. The results have expanded further application of nitrile and amide biotransformations in the synthesis of highly enantiopure carboxylic acids and their derivatives bearing a three-membered ring. We have also shown that 1-phenylaziridine-2-carboxamide undergoes readily the Lewis acid catalyzed ring-opening reactions with an azide, albeit in very low regioselectivity. Highly regioselective and enantiospecific ring-opening reaction of 1-phenylaziridine-2*S*-carboxamide was effected with benzyl bromide to afford a quantitative yield of *R*-β-[(benzyl)phenylamino]-α-bromopropanamide and *R*-α-[(benzyl)phenylamino]-β-bromopropanamide in a 10.5:1 ratio. The resulting ring-opening products, when treated with an N-nucleophilic reagent such as amine and azide, were transformed through dominantly the aziridinium intermediate into the optically active *S*-α-substituted-β-[(benzyl)phenylamino]propanamides in good yields.

Experimental Section

General Procedure for the Biotransformations of Nitriles or Amides. To an Erlenmeyer flask (150 mL) with a screw cap were added *Rhodococcus erythropolis* AJ270 cells[13,14a] (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 (2 mmol) 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 Table 1) by removing the biomass through a Celite pad filtration. The resulting aqueous solution was extracted with ethyl acetate. After drying ($MgSO_4$) and removing the solvent under a vacuum, the residue of the organic phase was chromatographed on a silica gel column using a mixture of petroleum ether and ethyl acetate as the mobile phase to give pure amide product **2**. The aqueous phase was freeze-dried (−50 to −60 °C), and the residue was treated with CH_2N_2 in ether below −15 °C. After filtration, ether was then removed from the solution under a vacuum and the residue was subjected to silica gel column chromatography using a mixture of petroleum ether and ethyl acetate as the mobile phase to give pure methyl ester **4**. All products were fully characterized by spectroscopic data and microanalyses (see Supporting Information). The absolute configurations of **4a** and **17** were determined by comparing the directions of their optical rotations with that of the authentic samples,[6f,25] and the absolute configurations of other esters **4** were assigned assuming that the introduction of a substituent on the benzene ring did not change the direction of optical rotation. Enantiomeric excess values were obtained from chiral HPLC analysis (see Supporting Information).

Biotransformations of racemic 1-phenylaziridine-2-carbonitrile **1a** gave *S*-(−)-1-phenylaziridine-2-carboxamide (**2a**) and methyl *R*-(+)-1-phenylaziridine-2-carboxylate (**4a**). **2a:** white solid; mp 146−147 °C [lit.[26] mp 145−146 °C (racemic)]; $[\alpha]^{25}_D$ −204° (*c* 1.0, $CHCl_3$); ee 96.2% (Chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.24−7.30 (m, 2H), 6.98−7.07 (m, 3H), 6.50 (br, 1H), 5.89 (br, 1H), 2.72 (dd, *J* = 3.0, 6.9 Hz, 1H), 2.47 (dd, *J* = 1.2, 3.0 Hz, 1H), 2.36 (dd, *J* = 1.2, 6.9 Hz, 1H); IR (KBr) ν 3321.8, 3158.8 ($CONH_2$), 1678.7 cm^{-1} (C═O). **4a:** oil; $[\alpha]^{25}_D$ +165° (*c* 1.5, CH_2Cl_2); ee 91.0% (Chiral HPLC analysis) [lit.[8] *S*-enantiomer $[\alpha]^{25}_D$ −173.2° (*c* 0.25, $CHCl_3$); ee 84%]; ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 6.99−7.03 (m, 5H), 3.80 (s, 3H), 2.80 (dd, *J* = 3.0, 6.0 Hz, 1H), 2.67 (dd, *J* = 1.2, 3.0 Hz, 1H), 2.31 (dd, *J* = 1.2, 6.0 Hz, 1H); IR (KBr) ν 1747.2 cm^{-1} (C═O). Kinetic resolution of racemic amide **2a** yielded *S*-(−)-**2a** in 54% yield with 98.2% ee and *R*-(+)-**4a** in 45% yield with 89.0% ee. Biotransformation of 15 mmol of racemic nitrile **1a** using 6 g wet weight whole cells yielded *S*-(−)-**2a** in 45% yield (1.1 g) with >99.5% ee and *R*-(+)-**4a** in 47% yield (1.2 g) with 85.2% ee.

(25) Goda, Y.; Suzuki, J.; Maitani, T.; Yoshihira, K.; Takeda, M.; Uchiyama, M. *Chem. Pharm. Bull.* **1992**, *40*, 2236.

(26) Kotera, K.; Motomura, M.; Miyazaki, S.; Okada, T.; Matsukawa, Y. *Tetrahedron* **1968**, *24*, 1727.

Ring-Opening Reaction of 1-Phenylaziridine-2-carboxamide with NaN_3 and $TMSN_3$. A mixture of (±)-1-phenylaziridine-2-carboxamide **2a** (0.5 mmol) and Lewis acid (0.1 mmol) in a specific solvent (10 mL) (Table 2) was stirred for 10 min at room temperature. A nucleophilic reagent was added, and the resulting mixture was kept stirring under conditions specified in Table 2. After completion of the reaction, which was monitored by TLC, water was added and extracted with ether. The organic phase was dried with anhydrous $MgSO_4$, and the solvent was removed under a vacuum. The residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate to give a mixture of **10** and **11**. Products **10** and **11** were inseparable from column chromatography, and their ratio was determined roughly by an ^{1}H NMR spectrum.

(±)-2-Azido-3-(phenylamino)propanamide (10) and 3-Azido-2-(phenylamino)propanamide (11) Were Obtained in a 3.1:1 Ratio. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) (**10**) δ 7.17−7.24 (m, 2H), 6.63−6.83 (m, 3H), 6.54 (br, 1H), 6.47 (br, 1H), 4.18−4.22 (dd, J = 4.5, 7.2 Hz, 1H), 4.15 (br, 1H), 3.75 (dd, J = 4.5, 13.6 Hz, 1H), 3.45 (dd, J = 7.3, 14.0 Hz, 1H); (**11**) δ 7.17−7.24 (m, 0.65H), 6.63−6.83 (m, 0.97H), 6.54 (br, 0.32H), 6.47 (br, 0.32H), 4.37 (br, 0.32H), 3.91−3.96 (m, 0.32H), 3.83−3.89 (m, 0.32H), 3.68−3.72 (m, 0.32H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) (**10**) δ 171.2, 146.6, 129.5, 118.6, 113.3, 62.6, 46.5; (**11**) δ 173.9, 145.9, 129.6, 119.7, 113.9, 58.1, 52.4.

Ring-Opening Reaction of *S*-1-Phenylaziridine-2-carboxamide with Benzyl Bromide. A mixture of *S*-(−)-1-phenylaziridine-2-carboxamide **2a** (0.5 mmol) and benzyl bromide (0.6 mmol) in acetonitrile (10 mL) was refluxed for 11 h until the starting **2a** was consumed, which was monitored by TLC. The solvent was removed under a vacuum, and the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate to give a mixture of *R*-3-[(benzyl)phenylamino]-2-bromopropanamide **13** and *R*-2-[(benzyl)phenylamino]-3-bromopropanamide **14** in a 10.5:1 ratio. Chiral HPLC analysis showed that both **13** and **14** were of >99.5% ee. ^{1}H NMR (300 MHz, $CDCl_3$, TMS) (**13**) δ 7.15−7.33 (m, 7H), 6.73−6.78 (m, 3H), 6.06 (br, 1H), 5.56 (br, 1H), 4.72(s, 2H), 4.54 (t, J = 7.0 Hz, 1H), 4.30 (dd, J = 7.3, 15.4 Hz, 1H), 3.91 (dd, J = 6.1, 15.4 Hz, 1H); (**14**) δ 7.15−7.33 (m, 0.67H), 6.78−6.90 (m, 0.29H), 6.06 (br, 0.09H), 5.54 (br, 0.09H), 4.72 (s, 0.20H), 4.52−4.57 (m, 0.09H), 4.10 (dd, J = 5.2, 11.0 Hz, 0.09H), 3.73 (dd, J = 8.3, 10.8 Hz, 0.09H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 170.3, 147.0, 138.2, 129.5, 128.6, 126.9, 117.7, 112.8, 55.8, 55.1, 45.0. Anal. Calcd for $C_{16}H_{17}BrN_2O$: C, 57.41; H, 5.10; N, 8.41. Found: C, 57.42; H, 5.12; N, 8.20.

General Procedure for the One-Pot Synthesis of Optically Active α,β-Diamino Amides 15 from *S*-1-Phenylaziridine-2-carboxamide. A mixture of *S*-(−)-1-phenylaziridine-2-carboxamide **2a** (0.5 mmol) and benzyl bromide (0.6 mmol) in acetonitrile (10 mL) was refluxed for 11 h until the starting **2a** was consumed, which was monitored by TLC. After cooling to room temperature, a nucleophilic reagent (2 mmol) was added and the resulting mixture was refluxed for another period of time (Table 3). The solvent was removed under a vacuum, and the residue was chromatographed on a silica gel column eluting with a mixture of petroleum ether and ethyl acetate to give pure α,β-diamino carboxamides **15a**−**d**.

***R*-(−)-3-[(Benzyl)phenylamino]-2-(benzylamino)propanamide (15a):** white solid; mp 110−111 °C; $[\alpha]^{25}_D$ −6.5° (*c* 0.93 CH_2Cl_2); ee 95.0% (Chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.13−7.29 (m, 12H), 7.08 (br, 1H), 6.78−6.87 (m, 3H), 5.41 (br, 1H), 4.51 (d, J = 16.9 Hz, 1H), 4.44 (d, J = 16.9 Hz, 1H), 3.70−3.83 (m, 2H), 3.46−3.56 (m, 3H), 1.61 (br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, TMS) δ 176.1, 148.8, 139.3, 138.2, 129.4, 128.7, 128.5, 128.0, 127.3, 127.1, 126.9, 118.2, 114.2, 61.1, 55.9, 54.8, 52.7; IR (KBr) ν 3343.6, 3317.0 ($CONH_2$), 3181.0 (N−H), 1680.7 cm^{-1} (C═O); MS (ESI) *m*/*z* (%) 359.9 (100) [M + H$^+$], 382.2 (6) [M + Na$^+$]. Anal. Calcd for $C_{23}H_{25}N_3O$: C, 76.85; H, 7.01; N, 11.69. Found: C, 76.48; H, 7.06; N, 11.45.

Conversion of 15 into *R*-(−)-2-Amino-3-(phenylamino)propanoic Acid 17. Under atmospheric hydrogen, a mixture of *R*-(−)-3-[(benzyl)phenylamino]-2-(benzylamino)propanamide **15a** (0.5 mmol) and Pd/C (10 mg) in methanol was stirred at room temperature for 4 h. After removal of Pd/C through Celite pad filtration and removal of solvent under a vacuum, the residue was heated with hydrochloric acid (6 N) at 80 °C for 6 h. The solvent was removed, and the residue was subjected to a cationic exchange resin column (Dowex, 50 × 8) followed by a reversed-phase ODS column (35−70 μm) to give pure *R*-(−)-2-amino-3-(phenylamino)-propanoic acid **17**: mp 134−136 °C; $[\alpha]^{25}_D$ −8.9° (*c* 0.45 H_2O/CH_3CN/TFA = 90:10:0.1); ee 85.7% (Chiral HPLC analysis) [lit.[25] *S*-enantiomer: $[\alpha]^{25}_D$ +2.5° (H_2O/CH_3CN/TFA = 90:10:0.1]; ^{1}H NMR (300 MHz, D_2O, TMS) δ 7.22−7.27 (m, 2H), 6.77−6.82 (m, 3H), 3.91 (dd, J = 4.2, 7.6 Hz, 1H), 3.65 (dd, J = 3.9, 12.0 Hz, 1H), 3.52 (dd, J = 8.0, 12.1 Hz, 1H), 2.43 (s, 3H); IR (KBr) ν 3422.1, 1636.3 cm^{-1} (C═O). When using *R*-(−)-2-azido-3-[(benzyl)phenylamino]propanamide **15d** as starting material, the reaction gave **17** with an ee of 63.8%.

Acknowledgment. We thank the Ministry of Science and Technology (2003CB716005, 2006CB806106), the National Natural Science Foundation of China, and the Chinese Academy of Sciences for financial support.

Supporting Information Available: Preparation of starting nitriles and their spectroscopic data, full characterization of products, ^{1}H and ^{13}C NMR spectra of **2**, **4**, **10**, **11**, and **13**−**17**, and HPLC analysis of all chiral products. This material is available free of charge via the Internet at http://pubs.acs.org.

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