JOC*Note*

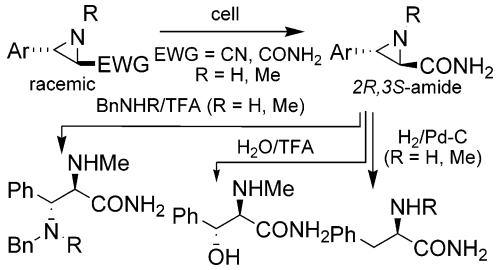
Nitrile and Amide Biotransformations for the Synthesis of Enantiomerically Pure 3-Arylaziridine-2-carboxamide Derivatives and Their Stereospecific Ring-Opening Reactions

Jin-Yuan Wang, De-Xian Wang, Jie Pan, Zhi-Tang Huang, and Mei-Xiang Wang*

Beijing National Laboratory for Molecular Sciences, Laboratory of Chemical Biology, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China

mxwang@iccas.ac.cn

Received August 7, 2007



Catalyzed by *Rhodococcus erythropolis* AJ270 (whole cell catalyst) under very mild conditions, a number of racemic *trans*-3-arylaziridine-2-carbonitriles and amides were efficiently transformed into enantiopure 2*R*,3*S*-3-arylaziridine-2-carboxamides. While the nitrile hydratase exhibits low selectivity against nitrile substrates, the amidase is highly enantioselective toward 2*S*,3*R*-3-arylaziridine-2-carboxamides. Upon the treatment with catalytic hydrogenation, amine, or water in the presence of one equivalent of TFA, the resulting aziridine-2-carboxamides underwent highly efficient and stereospecific ring-opening reactions to produce enantiopure α-amino-, α,*β*-diamino-, and α-amino-*β*-hydroxypropanamide derivatives in high yields.

Chiral aziridine-2-carboxylic acid derivatives, *C*-activated aziridine compounds, and 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] however, the synthesis of optically active aziridine-2-carboxylates still remains challenging to synthetic chemists.[5] Most chiral aziridine-2-carboxylates were prepared using either chiral starting materials[1b,2b,5] or chiral auxiliaries,[1b,2b,5] and most of them are generally time-consuming or not cost-effective. Although catalytic asymmetric syntheses have been reported,[2b,5] however, they are limited to a narrow substrate spectrum. A few advances in this field have been achieved very recently. For example, Cu(I)-catalyzed aziridination of cinnamates using a chiral 2,2′-bifuranyl-3,3′-diamine-derived C_2-diimide ligand has been reported to yield *trans*-3-aryl-1-tosylaziridine-2-carboxylates with 80.1−99% ee.[6] Using boron catalysts derived from vaulted chiral binaphthol and biphenanthrol ligands, aziridination of *N*-dianisylmethylimines (*N*-DAM-imines) with ethyl diazoacetate afforded *cis*-3-aryl(alkyl)-1-DAM-aziridine-2-carboxylates with ee's ranging from 63% to 97%.[7] While a catalytic aziridination of chalcones using a (+)-Tröger's base-derived aminimide as an NH-transfer reagent gave moderate enantioselectivity,[8] a chiral pyrrolidine-catalyzed aziridination of unsaturated aldehydes with acetyl hydroxycarbamate produced 1-Cbz-2-formylaziridines with dr 4:1−19:1 and 84−99% ee.[9] The lipase-mediated kinetic resolution of racemic 1-arylaziridie-2-carboxylates has been shown to give, in most cases, disappointingly low chemical yield and enantioselectivity.[10]

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 synthesis of not only the chemical commodities such as acrylamide and nicotinic acid but also chiral carboxylic acids and their amide 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

(1) (a) For a recent monograph, see: Yudin, A. K., Ed. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: New York, 2006. For recent reviews, see: (b) Osborn, H. M.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, *8*, 1693. (c) Xu, X. E. *Tetrahedron* **2004**, *60*, 2701. (d) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347.

(2) (a) For aziridine natural products, see: Lowden, P. P. Aziridine natural products: discovery, biological activity and biosynthesis. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: New York, 2006; Chapter 11. (b) For aziridinecarboxylates, see: Zhou, P.; Chen, B.-C.; Davis, F. A. Asymmetric syntheses with aziridinecarboxylate and aziridinephosphonate building blocks. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: New York, 2006; Chapter 3.

(3) For recent examples, see: (a) Denolf, B.; Mangelinkx, S.; Törnroos, K. W.; De Kimpe, N. *Org. Lett.* **2006**, *8*, 3129. (b) Lee, B. K.; Kim, M. S.; Hahm, H. S.; Kim, D. S.; Lee, W. K.; Ha, H.-J. *Tetrahedron* **2006**, *62*, 8393 and references therein. (c) Kokotos, C. G.; Aggarwal, V. K. *Org. Lett.* **2007**, *9*, 2099 and references therein.

(4) For a useful overview of the synthesis of chiral oxirane-2-carboxylic acid derivatives, see: Wang, M.-X.; Lin, S.-J.; Liu, C.-S.; Zheng, Q.-Y.; Li, J.-S. *J. Org. Chem.* **2003**, *68*, 4570 and references therein.

(5) For a useful overview of the synthesis of chiral aziridine-2-carboxylate derivatives, see: Wang, J.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Huang, Z.-T.; Wang, M.-X. *J. Org. Chem.* **2007**, *72*, 2040.

(6) Wang, X.; Ding, K. *Chem. Eur. J.* **2006**, *12*, 4568.

(7) Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185 and references cited therein.

(8) Shen, Y.-M.; Zhao, M.-X.; Xu, J.; Shi, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 8005.

(9) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Cordova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778.

(10) Kumar, H. M. S.; Rao, M. S.; Chakravarthy, P. P.; Yadav, J. S. *Tetrahedron: Asymmetry* **2004**, *15*, 127.

(11) For reviews, see: (a) Sugai, T.; Yamazaki, T.; Yokoyama, M.; Ohta, H. *Biosci. Biotechnol. Biochem.* **1997**, *61*, 1419 and references therein. (b) Martinkova, L.; Kren, V. *Biocatal. Biotransform.* **2002**, *20*, 73. (c) Wang, M.-X. *Top. Catal.* **2005**, *35*, 117.

(12) For recent examples, see: (a) Kamila, S.; Zhu, D.; Biehl, E. R.; Hua, L. *Org. Lett.* **2006**, *8*, 4429. (b) Bergeron, S.; Chaplin, D. A.; Edwards, J. H.; Ellis, B. S. W.; Hill, C. L.; Holt-Tiffin, K.; Knight, J. R.; Mahoney, T.; Osborne, A. P.; Ruecroft, G. *Org. Process Res. Dev.* **2006**, *10*, 661.

10.1021/jo701732h CCC: $37.00
Published on Web 10/25/2007

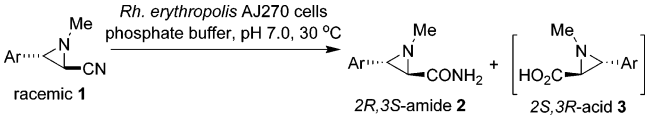
Rhodococcus erythropolis AJ270,[13] a nitrile hydratase/amidase-containing whole cell catalyst, is able to efficiently and enantioselectively transform a variety of racemic nitriles bearing an α-[14] or a *β*-stereocenter[15] and prochiral dinitriles[16] into highly enantiopure carboxylic acids and amides. Recently, we have found that biotransformations of nitriles bearing a cyclopropane[17] or an epoxide ring[4,18] proceeded in a highly predictable manner in terms of reaction efficiency and enantioselectivity based on the substituents and configurations of the substrates. Biotransformations of racemic 1-arylaziridine-2-carbonitriles have been found to follow the same reaction model, producing the corresponding enantiopure amide and acid products.[5] Interestingly, the same reaction using a nitrile-hydrolyzing *Rhodococcus* IFO15564 cell catalyst did not allow the isolation of acid product.[19] In order to explore the full scope of nitrile and amide biotransformations in the synthesis of *C*-activated enantiopure aziridine derivatives, and also to gain deep insight into the chiral recognition of the nitrile hydratase and the amidase involved in *Rhodococcus erythropolis* AJ270, we undertook the current study. Herein we report the highly efficient biocatalytic preparation of enantiopure *trans*-3-aryl-1-methylaziridine-2-carboxamides. Their stereospecific aziridine ring-opening reactions in the synthesis of α-amino-, α,*β*-diamino-, and α-amino-*β*-hydroxy acid derivatives will also be discussed.

We began our study by testing the biotransformation of racemic *trans*-1-methyl-3-phenylaziridine-2-carbonitrile **1a**. Prior to biocatalytic transformation, the configuration of 1-methyl group relative to *trans*-orientated phenyl and carboxamide groups was examined. The NOESY experiment (see Supporting Information) showed interaction between methyl protons and both protons of the aziridine ring, suggesting a very fast flipping of the methyl group between two sides of the three-membered ring, or a rapid inversion of the lone-pair elelctrons on the nitrogen in the NMR time scale. It was expected, therefore, that the steric feature of *trans*-3-aryl-1-methylaziridine-2-carbonitriles should be more or less similar to that of *trans*-2,2-dimethyl-3-phenylcyclopropanecarbonitrile, a type of good substrate for nitrile-hydrolyzing cells.[17b]

Catalyzed by *Rhodococcus erythropolis* AJ270 whole cell catalyst under very mild conditions, such as in an aqueous phosphate buffer with pH 7.0 at 30 °C, racemic *trans*-1-methyl-3-phenylaziridine-2-carbonitrile **1a** underwent a highly efficient and enantioselective hydrolysis. As shown in Table 1, nitrile **1a** was completely hydrated within minutes, and the 50% conversion of amide was also achieved around 40 min to give enantiopure **2a** in 45% yield (entry 1, Table 1). The biotransformations of 4-tolyl-substituted analogue **1b** proceeded equally well to produce enantiopure **2b** in an almost quantitative yield (entry 2, Table 1). Surprisingly, when a 4-methoxy group was introduced, substrate **1c** gave an almost optically inactive amide product **2c** (entry 3, Table 1). When substrates were bearing a halogen substituent on the benzene ring, the amidase-catalyzed amide hydrolysis exceeded the nitrile hydratase-catalyzed nitrile hydration reaction. For example, complete nitrile hydration of racemic **1d** did not allow the accumulation of amide product **2d** as the latter was rapidly hydrolyzed under the biocatalytic reaction conditions (entry 4, Table 1). To understand the enantioselectivity of the nitrile hydratase against *trans*-3-aryl-1-methylaziridine-2-carbonitriles, we quenched the hydration reaction of **1d**−**f** at its ca. 50% conversion (entries 5−7, Table 1). On the basis of the ee values (<5%−26%) of the recovered nitriles *2R*,3*S*-**1d**−**f**, it is concluded that the nitrile hydratase involved in *Rhodococcus erythropolis* AJ270 is less 2*S*,3*R*-enantioselective against aziridine-2-carbonitriles **1**. It is worth noting that, albeit in low ee (24%), the amide **2d** (26% yield) isolated from the same reaction turned out to be 2*R*,3*S*-configured. The outcomes indicate clearly that combination of a less 2*S*,3*R*-enantioselective nitrile hydratase and a highly 2*S*,3*R*-enantioselective amidase is responsible for the overall enantioselective nitrile biotransformations.

In the nitrile biotransformations depicted in Table 1, no corresponding *trans*-3-aryl-1-methylaziridine-2-carboxylic acids **3** were isolated because they were not stable under the reaction conditions. Interestingly, acids **3b** and **3c**, which contain an electron-donating group such as a methoxy or a methyl group on the benzene ring, underwent spontaneous decomposition to give mainly aromatic aldehyde compounds. Decomposition of other acids, however, gave rise to an inseparable mixture. Lyophilization of the reaction media followed by the treatment with CH_2N_2 and column chromatography led to the isolation

TABLE 1. Biotransformations of Racemic *trans*-3-Aryl-1-methylaziridine-2-carbonitriles 1[a]



entry	(±)-**1**	Ar	time (h)	**2** (%)[b]/ee (%)[c]	**1** (%)[b]/ee (%)[c]
1	**1a**	C_6H_5	0.7	45/ >99.5	−/ −
2	**1b**	4-Me−C_6H_4	1	48/ >99.5	−/ −
3	**1c**	4-MeO−C_6H_4	1.5	47/ <5	−/ −
4	**1d**	4-Br−C_6H_4	5	−/ −	trace/ <5
5	**1d**	4-Br−C_6H_4	1	26/ 24[d]	46/ 26[e]
6	**1e**	4-F−C_6H_4	1	−/ −	39/ 9.8
7	**1f**	4-Cl−C_6H_4	1.5	−/ −	42/ <5

[a] The racemic nitrile **1** (1 mmol) was incubated with *Rhodococcus erythropolis* AJ270 (2 g wet weight) in phosphate buffer (0.1 M, pH 7.0, 50 mL) at 30 °C. 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] Configurations of amide obtained are 2*R*,3*S*. [e] Configurations of nitrile recovered are 2*R*,3*S*.

(13) (a) Blakey, A. J.; Colby, J.; Williams, E.; O'Reilly, C. *FEMS Microbiol. Lett.* **1995**, *129*, 57. (b) O'Mahony, R.; Doran, J.; Coffey, L.; Cahill, O. J.; Black, G. W.; O'Reilly, C. *Antonie van Leeuwenhoek* **2005**, *87*, 221.

(14) (a) Wang, M.-X.; Lu, G.; Ji, G.-J.; Huang, Z.-T.; Meth-Cohn, O.; Colby, J. *Tetrahedron: Asymmetry* **2000**, *11*, 1123. (b) Wang, M.-X.; Li, J.-J., Ji, G.-J.; Li, J.-S. *J. Mol. Catal. B: Enzym.* **2001**, *14*, 77. (c) Wang, M.-X.; Zhao, S.-M. *Tetrahedron: Asymmetry* **2002**, *13*, 1695. (d) Wang, M.-X.; Lin, S.-J. *J. Org. Chem.* **2002**, *67*, 6542. (e) Wang, M.-X.; Lin, S.-J.; Liu, J.; Zheng, Q.-Y. *Adv. Synth. Catal.* **2004**, *346*, 439. (f) Wang, M.-X.; Liu, J.; Wang, D.-X. Zheng, Q.-Y. *Tetrahedron: Asymmetry* **2005**, *16*, 2409. (g) Liu, J.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Chin. J. Chem.* **2006**, *24*, 1665. (h) Ma, D.-Y.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *Tetrahedron: Asymmetry* **2006**, *17*, 2366.

(15) (a) Wang, M.-X.; Wu, Y. *Org. Biomol. Chem.* **2003**, *1*, 535. (b) Zhao, S.-M.; Wang, M.-X. *Chin. J. Chem.* **2002**, *20*, 1291. (c) Ma, D.-Y.; Zheng, Q.-Y.; Wang, D.-X.; Wang, M.-X. *Org. Lett.* **2006**, *8*, 3231. (d) Gao, M.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *J. Org. Chem.* **2006**, *71*, 9532.

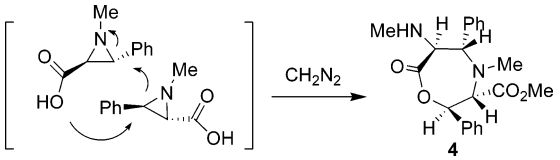
(16) Wang, M.-X.; Liu, C.-S.; Li, J.-S. *Tetrahedron: Asymmetry* **2001**, *12*, 3367.

(17) (a) Wang, M.-X.; Feng, G.-Q. *New J. Chem.* **2002**, 1575. (b) Wang, M.-X.; Feng, G.-Q. *J. Org. Chem.* **2003**, *68*, 621. (c) Wang, M.-X.; Feng, G. Q. *J. Mol. Catal. B: Enzym.* **2002**, *18*, 267. (d) Wang, M.-X.; Feng, G.-Q.; Zheng, Q.-Y. *Tetrahedron: Asymmetry* **2004**, *15*, 347.

(18) Wang, M.-X.; Deng, G.; Wang, D.-X. Zheng, Q.-Y. *J. Org. Chem.* **2005**, *70*, 2439.

(19) Moran-Ramallal, R.; Liz, R.; Gotor, V. *Org. Lett.* **2007**, *9*, 521.

SCHEME 1. Dimerization of Aziridine-2-carboxylic Acid 3

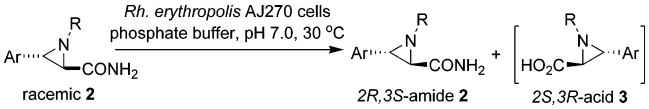


of compound **4**. The formation of **4** is most likely due to the dimerization of **3a** (Scheme 1).

Since the amidase appeared more efficient and enantioselective than the nitrile hydratase in overall nitrile biotransformations, we then investigated the *Rhodococcus erythropolis* AJ270-catalyzed kinetic resolution of racemic amides **2**. As illustrated in Table 2, except for the reaction of 4-methoxy-substituted substrate **2c** which gave virtually no enantiocontrol (entry 2, Table 2), racemic amide **2a** (entry 1, Table 2) and its analogues **2d**−**f** (entries 3−5, Table 2) bearing a 4-substituent other than methoxy on the benzene ring were efficiently resolved into enantiopure compounds in almost quantitative yields. An amide having a meta substituent on the benzene moiety was also accepted as an excellent substrate by the amidase. This has been exemplified by the highly efficient and enantioselective reaction of **2h** (entry 7, Table 2). The further move of the substituent to the ortho position on the benzene ring resulted in a significant drop of enantioselectivity (entry 6, Table 2). The racemic *trans*-3-phenylaziridine-2-carboxamide, **2i**, the substrate that is devoid of a methyl group on the nitrogen of aziridine, acted as an excellent substrate to afford enantiomerically pure 2*R*,3*S*-3-phenylaziridine-2-carboxamide, **2i**, in 47% yield (entry 8, Table 2). It is worth addressing that the biocatalytic reaction can be scaled up; a gram-scale biotransformation of **2a**, for example, produced enantiopure 2*R*,3*S*-1-methyl-3-phenylaziridine-2-carboxamide in an excellent yield (entry 9, Table 2).

Rhodococcus erythropolis AJ270 cells were also able to catalyze the hydration reaction of racemic *cis*-3-phenylaziridine-2-carbonitriles. For example, the ca. 50% conversion of nitriles **5a** and **5b** into the corresponding amides **6a** and **6b** was effected readily within 1−2 h. On the basis of the enantiomeric purity of the amide **6** and the nitrile **5** recovered, we found that the nitrile hydratase involved in *Rhodococcus erythropolis* AJ270

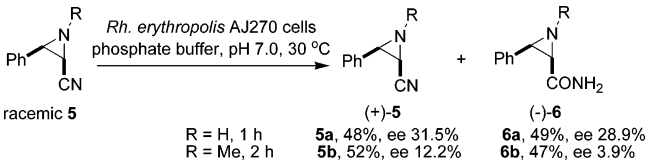
TABLE 2. Biotransformations of Racemic *trans*-3-Arylaziridine-2-carboxamides 2[a]



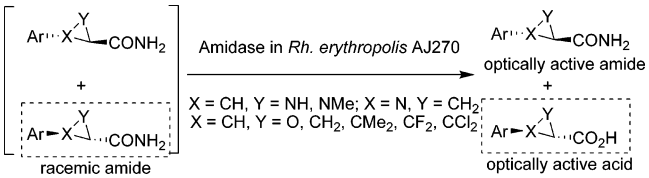
entry	(±)-**2**	R	Ar	time (h)	2*R*,3*S*-**2** yield (%)[b]	2*R*,3*S*-**2** ee (%)[c]
1	**2a**	Me	C_6H_5	0.33	48	>99.5
2	**2c**	Me	4-MeO−C_6H_4	1	40	<5
3	**2d**	Me	4-Br−C_6H_4	2	48	>99.5
4	**2e**	Me	4-F−C_6H_4	0.42	49	>99.5
5	**2f**	Me	4-Cl−C_6H_4	1	48	>99.5
6	**2g**	Me	2-Cl−C_6H_4	3.5	50	12
7	**2h**	Me	3-Cl−C_6H_4	3	46	>99.5
8	**2i**	H	C_6H_5	3	47	>99.5
9[d]	**2a**	Me	C_6H_5	4.8	48	>99.5

[a] The racemic amide **2** (1 mmol) was incubated with *Rhodococcus erythropolis* AJ270 (2 g wet weight) in phosphate buffer (0.1 M, pH 7.0, 50 mL) at 30 °C. Reaction time was optimized to roughly 50% conversion of the amide using HPLC analysis. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Racemic amide **2a** (12 mmol) was incubated with 6 g wet weight of microbial cells.

SCHEME 2. Biotransformations of Racemic *cis*-3-Phenylaziridine-2-carbonitriles



SCHEME 3. Enantioselection of the Amidase Involved in *Rhodococcus erythropolis* AJ270



displayed low enantioselectivity. Being different from racemic *trans*-3-phenylaziridine-2-carboxamides, the *cis*-configured amide analogues (±)-**6a** and (±)-**6b** were not accepted by the biocatalyst, giving no conversion of amide into acid in a lengthy incubation time (4 days).

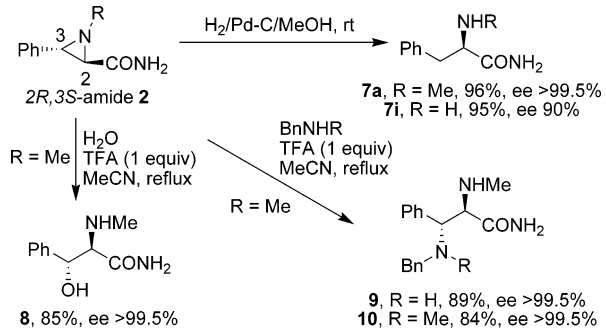
The outcomes of the current study are consistent with previous observations that nitrile hydratases are a type of highly active and less selective enzymes against a wide variety of nitrile substrates.[11c] These properties of the nitrile hydratase, such as having a broad substrate spectrum and possessing no or very little enantioselectivity, are intrinsically determined by its enzyme structure in which there is a spacious pocket near the active site.[17,18,20] In other words, a pair of enantiomers of 3-arylaziridine-2-carbonitriles are not recognized or differentiated by the nitrile hydratase, and almost identical biocatalytic hydration reactions were therefore effected.

The formation of highly enantiopure 2*R*,3*S*-3-arylaziridine-2-carboxamides from the overall biotransformations of racemic nitriles and from the kinetic resolution of racemic amide substrates indicated again that the amidase involved in *Rhodococcus erythropolis* AJ270 is an enantioselective enzyme. Moreover, careful scrutiny of the stereochemistries of all amide and acid products from the kinetic resolution of the corresponding amides containing a three-membered ring such as cyclopropane,[17] oxirane[4,18] or aziridine[5] reveals 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 three-membered ring, all racemic amides are kinetically resolved into the optically active amides and acids by the amidase following the same chiral selection model (Scheme 3). It fits well with the proposal[4,5,17,18] that the amidase in *Rhodococcus erythropolis* AJ270 might comprise a deeply buried and highly steric-demanding active site.

As a unique type of intermediate in organic synthesis, the ring-opening reactions of aziridines have attracted much attention. Compared to the nonactivated and *N*-activated aziridine compounds, however, the studies on the ring-opening reactions of *C*-activated aziridine derivatives are very limited. Previously, we[5] and others[19] have demonstrated that 1-arylaziridine-2-

(20) (a) Huang, W. J.; Jia, J.; Cummings, J.; Nelson, M.; Schneider, G.; Lindqvist, Y. *Structure* **1997**, *5*, 691. (b) Nagashima, S.; Nakasako, M.; Dohmae, N.; Tsujimura, M.; Takio, K.; Odaka, M.; Yohda, M.; Kamiya, N.; Endo, I. *Nat. Struct. Biol.* **1998**, *5*, 347. (c) Song, L.; Wang, M.; Shi, J.; Xue, Z.; Wang, M.-X.; Qian, S. *Biochem. Biophys. Res. Commun.* **2007**, *362*, 319.

SCHEME 4. Stereospecific Ring-Opening Reactions of Enantiopure Amides



carboxamides underwent highly regioselective ring-opening reactions at the 2-position with a number of *N*-nucleophiles. Having had enantiopure *trans*-3-arylaziridine-2-carboxamides (the typical *C*-activated aziridine derivatives) in hand, we explored their ring-opening reactions with emphasis on regio- and enantioselectivities. In the presence of Pd/C, **2a** (ee > 99.5%) and **2i** (ee > 99.5%) were hydrogenated readily to afford almost quantitatively *R*-2-(methyl)amino-2-phenylpropanamide **7a** (ee >99.5%) and **7i** (ee 90%), respectively. The absolute configuration was assigned on the basis of its optical rotation in comparison with that of authentic sample.[21] This has also allowed us to assign the absolute configuration of the aziridine product obtained from biotransformations. Being different from 1-arylaziridine-2-carboxamide in which the ring-opening reaction occurred at the 2-position,[5] 2*R*,3*S*-3-phenyl-1-methylaziridine-2-carboxamide, **2a**, underwent a Brønsted acid-promoted highly efficient and stereospecific ring-opening reaction at the 3-position with benzylamine and *N*-methyl(benzyl)amine to afford exclusively 3-benzylamino- and 3-benzyl(methyl)amino-2-methylamino-3-phenylpropanamides **9** and **10** in the yield of 89% and 84%, respectively (Scheme 4). Analogously, upon the treatment with water in the presence of one equivalent of trifluoroacetic acid (TFA), **2a** was transformed into 2-methylamino-3-hydroxy-3-phenylpropanamide **8** as the sole product in good yield. The clear-cut change of stereospecificity of the nucleophilic ring-opening reaction of aziridine-2-carboxamides from the 2- to the 3-position after the introduction of a phenyl into the 3-position originates most probably from the phenyl substituent which renders the 3-carbon (benzylic carbon) of the aziridine ring more electron-deficient than the 2-carbon. It is noteworthy that, except for the hydrogenation of **2i**, no racemization of either starting aziridine or products takes place in all of the ring-opening reactions (Scheme 4).

(21) Dallavalle, F.; Fisicaro, E.; Corradini, R.; Marchelli, R. *Helv. Chim. Acta* **1989**, *72*, 1479.
(22) Ayi, A. I.; Guedj, R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2045.
(23) Tack, J. W.; Lehmann, J.; Zymalkowski, F. *Arch. Pharm. (Weinheim, Ger.)* **1979**, 138.

In summary, we have provided a highly efficient and enantioselective synthesis of enantiopure 2*R*,3*S*-3-arylaziridine-2-carboxamides from the biotransformations of racemic nitriles and amides. While the nitrile hydratase exhibits low selectivity against nitrile substrates, the amidase is highly enantioselective toward 2*S*,3*R*-3-arylaziridine-2-carboxamides. The results have expanded further application of nitrile and amide biotransformations in the synthesis of highly enantiopure carboxamides bearing a three-membered ring. The resulting chiral aziridine-2-carboxamides act as reactive and versatile intermediates to undergo stereospecific ring-opening reactions to produce enantiomerically pure α-amino, α,*β*-diamino, and α-amino-*β*-hydroxypropanamide derivatives in excellent yields.

Experimental Section

General Procedure for the Biotransformations of Nitriles or Amides. To an Erlenmeyer flask (150 mL) with a screw cap was 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 amides (1 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 by removing the biomass through a Celite pad filtration. The resulting aqueous solution was extracted with ether. After drying ($MgSO_4$) and removing solvent under 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. All products were fully characterized by spectroscopic data and microanalyses. Enantiomeric excess values were obtained from chiral HPLC analysis (see Supporting Information).

General Procedure for the Ring-Opening Reaction of (*2R,3S*)-(−)-1-Methyl-3-phenylaziridine-2-carboxamide 2a. To a mixture of (*2R,3S*)-(−)-**2a** (0.5 mmol, ee > 99.5%) and CF_3COOH (0.5 mmol) in dry acetonitrile (10 mL) was added a nucleophilic reagent (0.6 mmol), and the resulting mixture was refluxed. After the starting material was consumed, which was monitored by TLC, the mixture was cooled to room temperature. The solvent was then removed under vacuum, and the residue was subjected to the basic alumina column chromatography, eluting with a mixture of methanol and ethyl acetate to give pure **8**−**10** (see Supporting Information).

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

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

JO701732H