JOC*Note*

Nitrile Biotransformation for Highly Enantioselective Synthesis of 3-Substituted 2,2-Dimethylcyclopropanecarboxylic Acids and Amides

Mei-Xiang Wang* and Guo-Qiang Feng

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

mxwang@infoc3.icas.ac.cn

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Abstract: Biotransformations of differently configured 2,2-dimethyl-3-substitued-cyclopropanecarbonitriles were studied using a nitrile hydratase/amidase-containing *Rhodococcus* sp. AJ270 whole-cell catalyst under very mild conditions. Although all of the *cis*-3-aryl-2,2-dimethylcyclopropanecarbonitriles appeared inert toward the biocatalyst, a number of racemic *trans*-isomers efficiently underwent a highly enantioselective hydrolysis to produce (+)-(1*R*,3*R*)-3-aryl-2,2-dimethylcyclopropanecarboxylic acids and (−)-(1*S*,3*S*)-3-aryl-2,2-dimethylcyclopropanecarboxamides in high yields with excellent enantiomeric excesses in most cases. The overall enantioselectivity of the biotransformations of nitriles originated from the combined effects of 1*R*-enantioselective nitrile hydratase and amidase, with the later being a dominant factor. The influence of the substrates on both reaction efficiency and enantioselectivity was discussed in terms of steric and electronic effects. Coupled with chemical transformations, biotransformations of nitriles provided convenient syntheses of optically pure geminally dimethyl-substituted cyclopropanecarboxylic acids and amides, including chrysanthemic acids, in both enantiomeric forms.

The chiral geminally dimethyl-substituted cyclopropyl group occurs in natural products[1] and synthetic pharmaceuticals[2] and agrochemicals.[3] Construction of optically active geminally dimethyl-substituted cyclopropyl structure, a remaining challenging task in organic synthesis, has been developed via (i) multistep synthesis starting from chiral substrates (chiral pool),[4,5] (ii) asymmetric synthesis utilizing a chiral auxiliary,[4,5] and (iii) catalytic asymmetric cyclopropanation of olefins with diazo compounds.[6] However, each method suffers from a few drawbacks. Whereas the first two approaches usually require lengthy multistep reactions and often give low overall yields, the last one often produces a mixture of two diastereomers and the control of both diastereoselectivity and enantioselectivity appears difficult. Enzymatic methods have also been explored; however, they are mainly limited to lipase- or esterase-catalyzed[7] hydrolysis of esters with only modest enantioselectivity. It was also reported that, in Lonza, the amidase was successfully utilized to resolve 2,2-dimethylcyclopropanecarboxamide.[8]

Biotransformations of nitriles,[9] through either a direct nitrilase-catalyzed conversion of a nitrile to a carboxylic acid[10] or a nitrile hydratase-catalyzed hydration of a nitrile followed by the hydrolysis of amide to acid by the action of the amidase,[11] have been demonstrated as being unique and environmentally benign methods for the synthesis of chiral carboxylic acids and their amide derivatives because of the excellent selectivity and very mild reaction conditions. Our earlier work has shown that *Rhodococcus* sp. AJ270, a robust nitrile hydratase/amidase-containing microorganism,[12] was able to hydrolyze a wide range of structurally diverse mono-[13] and dinitriles[14] with excellent chemo- and regioselectivieties. Very recently, we have found that *Rhodococcus* sp. AJ270 could efficiently and enantioselectively catalyze the hydrolysis of a number of racemic nitriles and prochiral dinitriles to produce enantiopure carboxylic acids and/or amides in high yields.[15] Our continuous interest in understanding reaction scope and applications of both nitrile hydratase and amidase involved in *Rhodococcus*

* To whom correspondence should be addressed. Phone: +8610-62554628. Fax: +8610-62569564.

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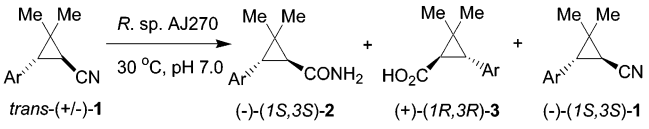
TABLE 1. Biotransformations of *trans*-(±)-3-Aryl-2,2-dimethylcyclopropanecarbonitriles 1[a]

					(1*S*,3*S*)-amide **2**		(1*R*,3*R*)-acid **3**		(1*S*,3*S*)-nitrile **1**	
entry	substrate	Ar	conc (mmol)	time	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)
1	**1a**	C_6H_5	1	4 h	53	33[d]	6	>99	40	99
2	**1a**	C_6H_5	1	12 h	32	59	43	>99	18	>99
3	**1a**	C_6H_5	1	33 h	29	>99	50	99	16	>99
4	**1a**	C_6H_5	0.5	30 h	48	>99	46	>99		
5	**1b**	4-F-C_6H_4	1	40 h	31	>99	49	82	12	86
6	**1b**	4-F-C_6H_4	0.5	65 h	43	>99	52	76		
7	**1c**	4-Cl-C_6H_4	1	80 h	29	>99	54	56	10	9
8	**1c**	4-Cl-C_6H_4	0.5	44 h	38	95	59	58	tr	
9	**1d**	3-Cl-C_6H_4	1	33 h	30	50	33	91	29	83
10	**1d**	3-Cl-C_6H_4	0.5	58 h	45	>99	52	80		
11	**1e**	2-Cl-C_6H_4	1	7 d	33	14	14	>99	43	0
12	**1e**	2-Cl-C_6H_4	0.5	7 d	74	15	20	>99		
13	**1f**	4-MeO-C_6H_4	1	16 h	36	93	40	96 (>99)[e]	15	10
14	**1f**	4-MeO-C_6H_4	1	23 h	45	>99	51	91		
15	**1g**	4-Me-C_6H_4	1	36 h	10	>99	49	81	33	83
16	**1g**	4-Me-C_6H_4	1	96 h	tr		53	84	30	81
17	**1h**	2-Me-C_6H_4	1	3 d	30	51	14	66	36	17
18	**1h**	2-Me-C_6H_4	1	7 d	41	25	26	74	24	4
19	**1h**	2-Me-C_6H_4	0.5	6 d	83	19	14	>99		

[a] Throughout the works in this Table, 2 g wet weight of *Rhodococcus* sp. AJ270 cells were used in 50 mL of phosphate buffer, and reaction conditions were not optimized. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] (+)-(1*R*,3*R*)-**2a** was obtained as favorable enantiomer. [e] After recrystallization.

SCHEME 1. Biocatalytic Hydrolysis of Racemic *trans*-2,2-Dimethyl-3-arylcyclopropanecarbonitriles 1



sp. AJ270 and in synthesizing enantiopure cyclopropane derivatives[16] led us to undertake the current study of biotransformation of 2,2-dimethyl-3-substituted-cyclopropanecarbonitriles. It is also hoped that the use of differently substituted and configurated cyclopropanecarbonitriles and amides as the substrates would allow us to probe the steric feature of the active site of the nitrile hydratase and amidase.

We first examined biotransformation of racemic *trans*-2,2-dimethyl-3-phenylcyclopropanecarbonitrile **1a**. Catalyzed by *Rhodococcus* sp. AJ270 cells under very mild conditions, nitrile (±)-**1a** underwent enantioselective hydrolysis to produce optically active products (Scheme 1). As summarized in Table 1, when the hydration of nitrile **1a** was terminated around 60% conversion, (−)-(1*S*,3*S*)-**1a** was obtained in excellent yield (40%) with excellent enantiomeric purity (99% ee). In addition, amide (+)-(1*R*,3*R*)-**2a** was isolated in 53% yield with enantiomeric excess of 33% (entry 1). The isolation of nitrile (−)-(1*S*,3*S*)-**1a** and the formation of amide (+)-(1*R*,3*R*)-**2a** in the initial period of incubation suggest the nitrile hydratase is 1*R*-enantioselective toward 2,2-dimethyl-3-phenylcyclopropanecarbonitrile. With the increase of incubation time, the conversion of nitrile hydration went to completion and the subsequent enantioselective hydrolysis of amide took place effectively to give optically active amide (−)-(1*S*,3*S*)-**2a** and acid (+)-(1*R*,3*R*)-**3a** (entries 2 and 3). Under controlled conditions with a lower substrate concentration, enantiopure amide **2a** and acid **3a** were prepared in almost quantitative yield from biotransformation of **1a** (entry 4).

To test the generality of the reaction and also to understand the substituent effect on the reaction, a number of racemic *trans*-3-aryl-2,2-dimethylcyclopropanecarbonitriles **1b**−**h** were synthesized[17] and subjected to *Rhodococcus* sp. AJ270. We have found that both the nature of and the substitution pattern of the substituent on the benzene ring showed intriguing effects on the conversion rate and enantioselectivity of nitrile hydration and amide hydrolysis reactions. Almost all nitriles bearing a *para*- or a *meta*-substituted aromatic group underwent efficient hydration on the cyano group and consecutive hydrolysis of amide to afford the corresponding (−)-(1*S*,3*S*) amides and (+)-(1*R*,3*R*) acids in excellent yields with good to excellent enantiomeric excesses (entries 5−10, 13 and 14). The presence of a 4-methoxy group seemed to facilitate the reaction leading to higher enantioselectivity (entries 13 and 14). Surprisingly, however, the introduction of a 4-methyl group resulted in sluggish nitrile hydration reaction, and the amide hydrolysis exceeded the nitrile hydration step. As a consequence, biotransformation of **1g** led to good yields of acid (+)-(1*R*,3*R*)-**3g** and nitrile (−)-(1*S*,3*S*)-**1g** together with only a small or trace amount of amide (−)-(1*S*,3*S*)-**2g** (entries 15 and16). In the case of 3-(2-chloro- or 2-methylphenyl)-2,2-dimethylcyclopropanecarbonitriles **1e** and **1h**, the biocatalytic hydrolysis proceeded very slowly. When the substrate concentration was halved and the hydration of the cyano group completed, the enantiopure acid was obtained, although the yield was less than 20% (entries 12 and 19). It should also be noted that the nitrile recovered from the reaction showed dramatically varied enantiomeric excesses depending upon the structure of the substrates. For the *ortho*-substituted and *para*-chloro-

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SCHEME 2. Kinetic Resolution of Racemic *trans*-2,2-Dimethyl-3-arylcyclopropanecarboxamides 2

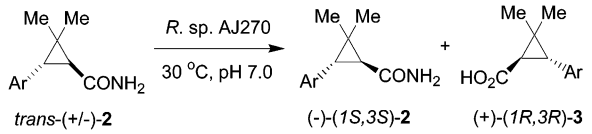

TABLE 2. Biocatalytic Kinetic Resolution of *trans*-3-Aryl-2,2-dimethylcyclopropanecarboxamides

				(1*S*,3*S*)-amide **2**		(1*R*,3*R*)-acid **3**	
entry	substrate	Ar	time[a]	yield[b] (%)	ee[c] (%)	yield[b] (%)	ee[c] (%)
1	**2a**	C_6H_5	73 h	46	>99	52	92
2	**2b**	4-F-C_6H_4	52 h	40	>99	57	67
3	**2c**	4-Cl-C_6H_4	48 h	30	67	65	31
4	**2d**	3-Cl-C_6H_4	84 h	44	91	49	74
5	**2e**	2-Cl-C_6H_4	6 d	85	<5	13	80
6	**2f**	4-MeO-C_6H_4	25 h	45	>99	52	88
7	**2g**	4-Me-C_6H_4	44 h	49	80	47	57
8	**2h**	2-Me-C_6H_4	7 d	70	39	26	95
9	**2h**	2-Me-C_6H_4	7 d[d]	68	42	28	>99

[a] Racemic amides **2** (0.5 mmol) were incubated with *Rhodococcus* sp. AJ270 (2 g wet weight) in phosphate buffer. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] 2 mL of methanol was added.

and methoxy-substituted substrates, the nitriles recovered were almost optically inactive (entries 7, 11, 13, and 18).

To shed further light on the stereochemistry of the biotransformation of nitriles **1**, racemic *trans*-3-aryl-2,2-dimethylcyclopropanecarboxamides **2** were prepared[18] and their biohydrolysis was investigated. Under identical catalytic conditions, amide (±)-**2** underwent a kinetic resolution process to give enantiomerically enriched amide (−)-(1*S*,3*S*)-**2** and acid (+)-(1*R*,3*R*)-**3** (Scheme 2). As illustrated in Table 2, the similar effects of the substituent and substitution pattern on the reactivity and enantioselectivity of the amidase, which were found from biotransformation of nitriles **1** (Table 1), were observed. It should be addressed that the relatively lower enantiomeric excesses obtained for (+)-(1*S*,3*S*)-**2** and (−)-(1*R*,3*R*)-**3** from kinetic resolution of (±)-**2** suggested that the enantioselectivity of the biotransformation of nitriles **1** originated from the combined action of (1*R*)-enantioselective nitrile hydratase and (1*R*)-enantioselective amidase, with the later being a dominant one.

Encouraged by the abovementioned results, we then tested the biotransformation of racemic *cis*-2,2-dimethyl-3-arylcyclopropanecarbonitriles **4**.[17] In sharp contrast to an effective biotransformation of racemic *trans*-2,2-dimethyl-3-arylcyclopropanecarbonitriles **1**, no hydrolysis of nitriles **4** was observed under the same conditions. Even a longer period (7 days) of interaction with *Rhodococcus* sp. AJ270 led to only the recovery of the starting nitriles.

In our previous study[16] we have found that biotransformations of *trans*-2-arylcyclopropanecarbonitriles proceeded rapidly with modest enantiocontrol whereas *cis*-2-arylcyclopropanenitriles underwent very slow biohydrolysis but with excellent enantioselection. We have proposed that a readily reachable reactive site be embedded within

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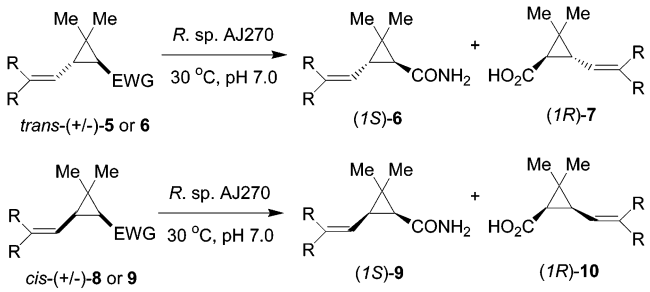
SCHEME 3. Biotransformation of Racemic Chrysanthemic Nitriles and Amides



the spacious pocket of the enantioselective nitrile hydratase while the amidase comprised a relatively deep-buried and size-limited enentioselective active site. The outcomes of the current study further support the hypotheses of action of both the nitrile hydratase and the amidase. Compared to *trans*-2-arylcyclopropanecarbonitriles and *trans*-2-arylcyclopropanecarboxamides, *trans*-2,2-dimethyl-3-arylcyclopropanecarbonitriles **1** and *trans*-2,2-dimethyl-3-arylcyclopropanecarboxamides **2** have increased steric hindrance around the cyano and amido group, respectively. Therefore, the interactions of these geminally dimethylated cyclopropanecarbonitrile and amide substrates with the active sites of the nitrile hydratase and amidase, respectively, should be slower but more stereoselective than their 2-arylcyclopropanecarbonitrile and amide analogues. These were indeed exemplified by the observation of slower reaction rate with much increased enantioselectivity for both nitrile hydration and amide hydrolysis in comparison to the biotransformation of racemic *trans*-2-arylcyclopropanecarbonitriles. Introduction of geminally substituted dimethyl groups into the cyclopropane skeleton further increased the bulkiness of already sterically crowded *cis*-configurated 2-arylcyclopropanecarbonitrile and amide molecules, and as a consequence the enzymatic reaction was completely inhibited.

On the basis of the results obtained, it can be concluded that the efficient and highly enantioselective biotransformation of cyclopropanecarbonitriles and amides is predominantly governed by the steric effect of both substituents attached to the 2- and 3-positions of cyclopropane ring. In other words, the reactivity and enantioselectivity of enzymatic hydrolysis of cyclopropanecarbonitriles and amides can be regulated by tuning the substituents either on the 2- or 3-position or on both positions of the three-membered ring. This may also allow us to envisage an efficient and highly enantioselective hydrolysis of 2,2-dimethylcyclopropanecarbonitrile or amide bearing a 3-substituent sterically smaller than a phenyl group. To test the validity of this predication and to prepare optically active chrysanthemic acids,[3] the hydrolysis of chrysanthmic nitriles was studied.

As we expected, all chrysanthemic nitriles[19] **5** and **8** tested underwent effective biohydrolysis to produce optically active chrysanthemic acids **7** and **10** and amides **6** and **9** (Scheme 3). In the case of racemic *trans*-configurated nitriles **5** and amides **6**, the biotransformations

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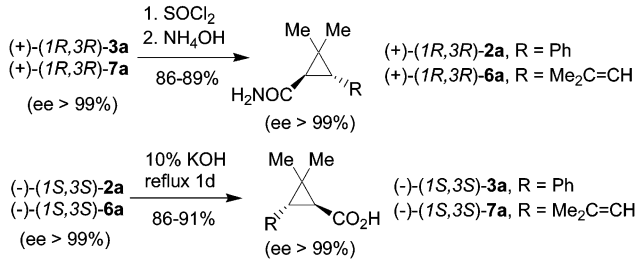
TABLE 3. Biotransformation of Chrysanthemic Nitriles and Amides

entry	substrate	EWG	R	time (h)[a]	**6** or **8** (yield,[b] ee[c])	**7** or **9** (yield,[b] ee[c])
1	(±)-**5a**	CN	Me	82	**6a** (48, >99)	**7a** (49, >99)
2	(±)-**5b**	CN	Cl	46	**6b** (45, >99)	**7b** (53, 81)
3	(±)-**6a**	$CONH_2$	Me	73	**6a** (48, >99)	**7a** (51, 97)
4	(±)-**6b**	$CONH_2$	Cl	48	**6b** (47, >99)	**7b** (48, 89)
5	(±)-**8a**	CN	Me	65[d]	**9a** (12, >99)	**10a** (48, >99)
6	(±)-**8b**	CN	Cl	46[e]	**9b** (29, >99)	**10b** (47, >99)
7	(±)-**9a**	$CONH_2$	Me	66	**9a** (48, >99)	**10a** (49, 97)
8	(±)-**9b**	$CONH_2$	Cl	48	**9b** (48, >99)	**10b** (47, 95)

[a] Racemic nitriles or amides (0.5 mmol) were incubated with *Rhodococcus* sp. AJ270 (2 g wet weight) in phosphate buffer. [b] Isolated yield (%). [c] Determined by chiral HPLC analysis (%). [d] 25% of (−)-nitrile **8a** were recovered. [e] 9% of nitrile **8b** were recovered.

SCHEME 4. Chemical Transformations of Amides and Acids



were very efficient and highly enantiopure products were afforded in quantitative yields (entries 1−4 in Table 3). Though less efficient than their *trans*-isomers, the *cis*-configurated nitrile **8** and amide **9** analogues also underwent high bioconversion to yield almost enantiopure acids **10** and amides **9** (entries 5−8 in Table 3). It is interesting to point out that the nitriles and amides containing a geminal dichlorovinyl moiety appeared to be more suitable substrates than those bearing a geminal dimethylvinyl substituent, indicating again that the enzymes involved in cells are mainly size selective.

To further show the utility of biotransformations of nitriles in the preparation of both antipodes of enantiomers, acids (+)-(1*R*,3*R*)-**3a** and -**7a** and amides (−)-(1*S*,3*S*)-**2a** and -**6a** were converted in excellent yields into amides (+)-(1*R*,3*R*)-**2a** and -**6a** and acids (−)-(1*S*,3*S*)-**3a** and -**7a**, respectively, using conventional chemical means. No racemization was observed during the functional group transformations (Scheme 4).

In conclusion, we have shown that *Rhodococcus* sp. AJ270 cells effectively catalyzed the hydrolysis of racemic *trans*-3-aryl-2,2-dimethylcyclopropanecarbonitriles under very mild conditions to form (1*R*,3*R*)-2,2-dimethyl-3-arylcyclopropanecarboxylic acids and (1*S*,3*S*)-2,2-diemthyl-3-arylcyclopropanecarboxamides in excellent yields with high enantiomeric excesses. The overall enantioselectivity of biotransformations of nitriles originated from the combined effects of a higher 1*R*-enantioselective amidase and a 1*R*-enantioselective nitrile hydratase involved in microbial cells. We have also demonstrated that the catalytic efficiency and enantioselectivity of both nitrile hydratase and amidase were strongly determined by both the configuration and the nature of the substituents. The presence of a 3-substituent smaller than an aryl group, either transoid or cisoid to the cyano or amido functional moiety with the molecule, facilitated the biohydrolysis with excellent enantioselectivity, which has been exemplified by the efficient preparation of highly enantiopure chrysanthemic acids from the biotransformations of chrysanthemic nitriles and amides. Coupled with facile chemical transformations, this biotransformation process provided effective and convenient syntheses of optically geminally dimethyl-substituted cyclopropanecarboxylic acids and amides in both enantiomeric forms.

Experimental Section[20]

All racemic nitriles **1**,[17] **4**,[17] **5**,[19] and **8**[19] and amides **2**,[18] **6**,[19] and **9**[19] were prepared following the literature methods. The configurations of optically active products were determined by conversion into known compounds followed by comparison of their sign of optical rotation with that of authentic samples.[21] All enantiomeric excess values were obtained from HPLC analysis with use of Chiralcel OD and OJ and Chiralpak AD columns (see Supporting Information).

General Procedure for Biotransformations of Nitriles and Amides. To an Erlenmeyer flask (100 mL) with a screw cap were added *Rhodococcus* sp. AJ270 cells[12,13] (2 g wet weight) and potassium phosphate buffer (0.1 M, 50 mL), and the resting cells were activated at 30 °C for 30 min with orbital shaking. Racemic nitriles or amides were added in one potion to the flask, and the mixture was incubated at 30 °C with the use of an orbital shaker (200 rpm). The reaction, monitored by TLC, 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 basified to pH 12 with aqueous NaOH (2 M). Extraction with ethyl acetate gave, after drying and concentration, the amides and unconverted nitriles. Separation of amide and nitrile was effected by column chromatography. The aqueous solution was then acidified using aqueous HCl (2 M) to pH 2 and extracted with ethyl acetate. Acid was obtained after removal of the solvent. All products were characterized by their spectra data and comparison of the melting points and optical rotary power with that of the known compounds or by full characterization (see Supporting Information).

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Supporting Information Available: Preparation of racemic nitriles and amides; details of characterization of nitriles, amides, and acids; results of biocatalytic kinetic resolution of amides; chemical transformations of acids and amides; and HPLC analysis of amides, acids, and nitriles. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) General experiment information was given in ref 15a.

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