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Biotransformations of Racemic 2,3-Allenenitriles in Biphasic Systems: Synthesis and Transformations of Enantioenriched Axially Chiral 2,3-Allenoic Acids and Their Derivatives

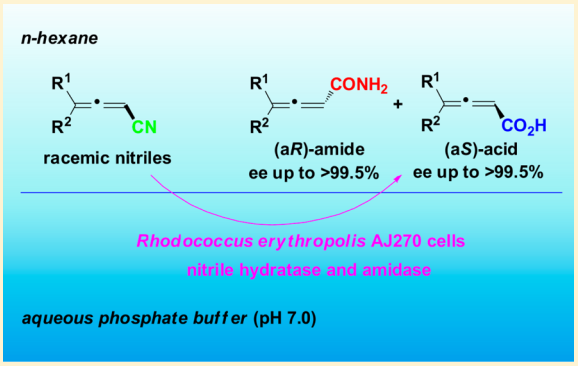
Yu-Fei Ao,[†] De-Xian Wang,[†] Liang Zhao,[‡] and Mei-Xiang Wang*[,‡]

[†]Beijing National Laboratory for Molecular Sciences, CAS Key Laboratory of Molecular Recognition and Function, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

[‡]Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology, Ministry of Education, Tsinghua University, Beijing 100084, China

Supporting Information

ABSTRACT: Catalyzed by *Rhodococcus erythropolis* AJ270 whole cells in an aqueous phosphate buffer−*n*-hexane biphasic system, racemic axially chiral 2,3-allenenitriles underwent hydrolysis to afford enantioenriched (a*R*)-2,3-allenamides and (a*S*)-2,3-allenoic acids with ee's up to >99.5%. Overall biotransformations proceeded through the nitrile hydratase-catalyzed efficient but nonselective hydration of nitriles followed by the amide hydrolysis catalyzed by the substrate-dependent enantioselective amidase. The application of the method has been demonstrated by the transformations of the resulting allene products into highly functionalized heterocyclic compounds with axial chirality of reactants being entirely transferred into or expressed as point chirality of products.



INTRODUCTION

As cumulative diene species, allenes and their derivatives have now become powerful and versatile entities in organic synthesis.[1] One of the unique features of allenes is their axial chirality. The molecular symmetry is broken when substituents are introduced properly into a parent allene skeleton. In contrast to a vast majority of literatures that report the synthetic applications of allene derivatives, it is quite noticeable that the use of optically active axially chiral allenes in synthesis has been rare.[1,2] This scarcity is attributable mainly to the lack of general methods for the preparation of enantiopure allene compounds, a formidable challenge faced by synthetic chemists.[1f,3,4] As functionalized allenes, 2,3-allenoic acids and their derivatives[5] are highly useful intermediates in the synthesis of diverse organic compounds. Unfortunately, the accessibility to these important building blocks in enantiomerically pure form is still limited.[6] For instance, enantiopure precursors are required in the synthesis of 2,3-allenoic acids and derivatives through so-called central-to-axial chirality transfer reactions.[7−9] While organocatalytic kinetic resolution is confined to 1,3-dipolar cycloaddition of 2,3-allenoates,[10] kinetic resolutions through biocatalytic hydrolysis of 2,3-allenoates give moderate to good enantioselectivity.[11] Until very recently, catalytic asymmetric syntheses of axially chiral 2,3-allenoates have been scatteringly reported.[12] It is therefore highly desirable to develop new synthetic methods and to provide enantioenriched novel 2,3-allenoic acids and their derivatives.

Biotransformations of nitriles proceed through either the nitrilase-catalyzed direct conversion of nitriles into carboxylic acids or the nitrile hydratase-catalyzed hydration of nitriles followed by the amidase-effected amide hydrolysis.[13] Nitrile biotransformations have become attractive methods in organic synthesis because of high biocatalytic efficiency, excellent selectivity, and environmentally benign conditions.[14] Studies have also demonstrated convincingly that biotransformations of nitriles complement the existing asymmetric chemical and enzymatic methods for the synthesis of chiral carboxylic acids and their derivatives.[15] It is especially worth noting that, in comparison with enzymatic ester hydrolysis, one distinct feature of biocatalysis of nitrile is the straightforward generation of enantiopure amides, which are invaluable compounds in synthetic chemistry, in addition to the formation of enantiopure carboxylic acids. Among a few widely used nitrile-hydrolyzing biocatalysts,[14,15] *Rhodococcus erythropolis* AJ270 is a nitrile hydratase and amidase-containing microbial whole cell catalyst.[16] The versatility of this whole-cell biocatalyst has been exemplified by enantioselective biotransformations of a large number of structurally diverse racemic nitriles including functionalized nitriles and (hetero)cyclic nitriles to produce highly enantiopure carboxylic acid and amide products.[13,17] It has been also revealed that while the nitrile hydratase exhibits low or virtually no enantioselectivity, the amidase is highly

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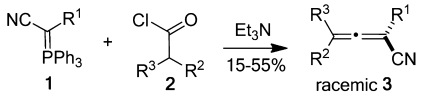
enantioselective.[13,17] The amidase has been therefore utilized recently to achieve enantioselective desymmetrization of prochiral[18] and meso dicarboxamides.[19]

Our continuous interest in developing synthetic biocatalysis of nitriles and amides led us to investigate the enantioselective biotransformations of axially chiral nitriles and amides. We report herein the *Rhodococcus erythropolis* AJ270 whole-cell catalyzed transformations of racemic 2,3-allenenitriles in biphasic systems. The reaction afforded enantioenriched 2,3-allenamides and 2,3-allenoic acids in good yields with enantiomeric excess values up to >99.5%. To the best of our knowledge, the study represents the first successful example in enantioselective biotransformations of axially chiral nitriles, as the very first attempt of biocatalytic hydrolysis of racemic 4-ethyl-4-methyl-2,3-allenenitrile gave appallingly low conversion and no enantioselectivity.[20] Synthetic potential of the resulting chiral allene derivatives is demonstrated by the synthesis of densely functionalized heterocyclic compounds from highly diastereoselective intramolecular bromolactamization and cycloaddition reactions with furan and azomethine ylide. In all cases, axial chirality of allenes is fully expressed as point chirality (stereogenic center) in products.

RESULTS AND DISCUSSION

Racemic 2,3-allenenitriles **3** were prepared from the reaction between α-haloalkanenitrile-derived ylides **1** and acyl chlorides **2** in the presence of triethylamine following a literature method[21] (Scheme 1). Moderate chemical yields were obtained because reaction always gave alkyne as a byproduct.

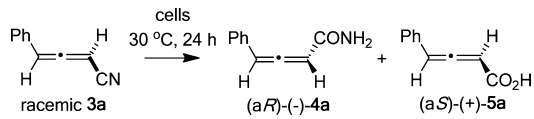
Scheme 1. Preparation of Racemic 2,3-Allenenitriles 1a−l



3a, R^1=R^2=H, R^3=Ph; **3b**, R^1=R^2=H, R^3=Bn;
3c, R^1=R^2=H, R^3=Ph$(CH_2)_2$;
3d, R^1=R^2=H, R^3=*c*-$C_6H_{11}CH_2$;
3e, R^1=Me, R^2=H, R^3=Bn;
3f, R^1=H, R^2=Me, R^3=Ph; **3g**, R^1=H, R^2=Me, R^3=Bn;
3h, R^1=R^2=H, R^3=Allyl; **3i**, R^1=R^2=H, R^3=*n*-Pr.

We first examined the biotransformations of nitrile **3a** under standard biocatalytic conditions. Thus, racemic 4-phenyl-2,3-allenenitrile **3a** was incubated with *Rhodococcus erythropolis* AJ270 whole cells[16] at 30 °C in neutral aqueous phosphate buffer. Unfortunately, the desired amide and acid products were obtained only in very low yields. Instead of enzymatic hydrolysis, allenenitrile **3a** underwent rapid and predominant dimerization reactions to give a mixture of diastereoisomers as reported previously in literature.[22] Dimerizations were not enzymatic processes, as in the absence of whole-cell catalyst dimerizations occurred spontaneously in aqueous phosphate buffer (entries 1 and 2, Table 1). Since allenenitrile **3a** was stable in organic media as it was prepared, dimerizations of **3a** were most probably promoted by water. Assuming the nitrile hydratase within *Rhodococcus erythropolis* AJ270 is active against substrate **3a** and it is able to tolerate organic solvents, effective biotransformations in aqueous and organic biphasic systems[23] would be anticipated. To test this working hypothesis, we then attempted biotransformations in biphasic systems. To create a biphasic system, several water-immiscible solvents were optimized except ethyl acetate and chloroform that are harmful

Table 1. Optimization of Biotransformations of Racemic Nitrile 3a[a]



entry	solvent + additive	volume (mL)	**4a** (%)[b]	ee (%)[c]	**5a** (%)[b]	ee (%)[d]	dimer (%)[b]
1[e]	–	–	18	92.0	17	90.0	55
2[f]	–	–	–	–	–	–	91
3	toluene	20	trace	–	–	–	87
4	MTBE	20	–	–	–	–	85
5	*n*-octane + ether	18 + 2	40	84.0	29	90.6	22
6	*c*-hexane + ether	18 + 2	–	–	–	–	88
7	*n*-hexane + ether	18 + 2	35	94.8	37	90.2	19
8	*n*-hexane + ether	9 + 1	35	90.1	34	88.5	22
9	*n*-hexane + ether	27 + 3	37	93.2	36	90.4	19
10	*n*-hexane + ether	45 + 5	37	88.2	32	89.4	18
11[f]	*n*-hexane + ether	18 + 2	–	–	–	–	25

[a]A mixture of substrate **3a** (1 mmol), ether, and organic solvent was injected into the suspension of *Rhodococcus erythropolis* AJ270 (2 g wet weight) in neutral phosphate buffer (0.1 M, 50 mL), and then the mixture was incubated at 30 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Determined by chiral HPLC analysis of methyl ester **5a**′, which was obtained efficiently from the reaction with CH_2N_2. [e]The reaction was performed for 4 h. [f]In the absence of whole cell biocatalyst.

to microbial cells. A small amount of diethyl ether (10%) was also added to increase the solubility of nitrile in alkanes. As summarized in Table 1, in biphasic systems that use toluene or methyl *t*-butyl ether (MTBE) as organic phase, almost no hydrolysis of nitrile was observed after 24 h (entries 3 and 4, Table 1). When cyclohexane was used as organic phase, biotransformations did not take place either (entry 6, Table 1). In all these cases, a mixture of dimers derived from **3a** was formed in high yields in 24 h. Although the dimerization reactions proceeded slower than in pure aqueous buffer, the presence of organic solvents employed had pronouncedly a detrimental effect on catalytic activity of the nitrile hydratase. To our delight, allenenitrile **3a** underwent biocatalytic hydrolysis in a mixture of aqueous phosphate buffer and *n*-hexane or *n*-octane with diethyl ether as an additive (entries 5 and 7, Table 1). Except for the formation of dimers in about 20% yield, all starting material was transformed into (a*R*-(−)-4-phenyl-2,3-allenamide **4a** and (a*S*)-(+)-4-phenyl-2,3-allenoic acid **5a**[24] in good yields and with high enantiomeric excess values (ee) of 94.8 and 90.2%, respectively (entry 7, Table 1). Gratifyingly, both 2,3-allenamide and 2,3-allenoic acid products were stable, and they did not form dimeric compounds under the reaction conditions. In terms of chemical yields of products, the amidase involved in *Rhodococcus erythropolis* AJ270 showed slightly higher enzyme activity in a biphasic buffer-*n*-hexane system than in a buffer-*n*-octane mixture (entries 5 and 7, Table 1). Variation of the volume of organic phase from 10 to 50 mL did not remarkably influence performance of both the nitrile hydratase and the amidase within microbial cells, as only marginal differences in chemical yields and ee values of the

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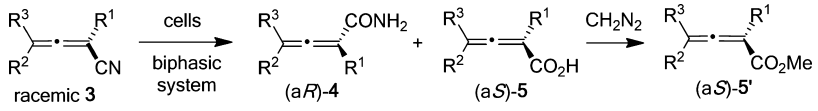
Table 2. Biotransformations of Racemic Nitriles 3[a]



entry	3	t (h)	4 (%)[b] (ee %)[c]	5 (%)[b] (ee %)[d]
1[e]	**3a** ($R^1 = R^2 = H$, $R^3 = Ph$)	5	**4a** (32) (61.2)	**5a** (11) (90.2)
2[f]	**3a** ($R^1 = R^2 = H$, $R^3 = Ph$)	24	**4a** (35) (94.8)	**5a** (37) (90.2)
3	**3b** ($R^1 = R^2 = H$, $R^3 = Bn$)	6.5	**4b** (49) (80.6)	**5b** (49) (84.2)
4	**3c** ($R^1 = R^2 = H$, $R^3 = Ph(CH_2)_2$)	6.5	**4c** (45) (49.8)	**5c** (51) (49.0)
5	**3d** ($R^1 = R^2 = H$, $R^3 = c$-HexCH_2)	44	**4d** (54) (15.8)	**5d** (44) (26.0)
6[g]	**3e** ($R^1 = Me$, $R^2 = H$, $R^3 = Bn$)	120	**4e** (−)	**5e** (−)
7[h]	**3f** ($R^1 = H$, $R^2 = Me$, $R^3 = Ph$)	72	**4f** (39) (>99.5)	**5f** (38) (>99.5)
8	**3g** ($R^1 = H$, $R^2 = Me$, $R^3 = Bn$)	7	**4g** (42) (43.4)	**5g′** (50)[i] (48.4)
9[j]	**3h** ($R^1 = R^2 = H$, $R^3 = Allyl$)	96	**4h** (91) (2.2)	**5h** (−)
10[k]	**3i** ($R^1 = R^2 = H$, $R^3 = n$-Pr)	96	**4i** (90) (3.2)	**5i** (−)

[a]A mixture of substrate **3** (1 mmol), ether, and *n*-hexane was injected into the suspension of *Rhodococcus erythropolis* AJ270 (2 g wet weight) in neutral phosphate buffer (0.1 M, 50 mL), and then the mixture was incubated at 30 °C. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Determined by chiral HPLC analysis of methyl esters **5′**, which were obtained efficiently from the reaction with CH_2N_2. [e]Optically inactive nitrile **3a** (38%, 2.6% ee) was recovered. [f]Dimer of **3a** (19%) was formed. [g]Starting nitrile **3e** (93%) was recovered. [h]Dimer of **3f** (18%) was formed. [i]Without isolation and purification, acid product **5g** was converted directly into methyl ester **5g′** after biocatalytic reaction. [j]The nitrile **3h** was hydrated completely in 2 h. [k]The nitrile **3i** was hydrated completely in 2.5 h.

products were yielded (entries 8−10, Table 1). It should be addressed that effective biotransformations of allenenitrile **3a** in a biphasic system indicate clearly the inhibition of spontaneous dimerization of allenenitrile. This has been exemplified by a control experiment from which dimeric products were obtained in 25% yield (entry 11, Table 1). More importantly, *Rhodococcus erythropolis* AJ270 whole-cell catalyst or the nitrile hydratase and amidase involved are stable in a biphasic system of buffer and *n*-hexane or *n*-octane, showing high enzymatic activity and good enantioselectivity.

Encouraged by the highly enantioselective biotransformations of **3a** in aqueous buffer−*n*-hexane biphasic media, a number of racemic 2,3-allenenitriles **3b−i** (Scheme 1) were subjected to biocatalytic transformations (Table 2). To facilitate the determination of enantiomeric excess values of products, 2,3-allenoic acids were converted almost quantitatively into their methyl esters using CH_2N_2. As monitored by TLC analysis, we found that all nitrile substrates tested were completely hydrated within 2 to 10 h to give virtually optically inactive 2,3-allenamides. It is worth mentioning that 2,3-allenamides are difficult to prepare by other synthetic methods. Chemical hydration of 2,3-allenenitriles, for example, did not lead to amides because of the lability of starting nitriles under chemical hydrolytic reaction conditions.[25] To understand the enantioselectivity of the nitrile hydratase toward racemic axially chiral 2,3-allenenitriles, the biocatalytic hydration of **3a** was quenched when about a half amount of starting nitrile was consumed. The ee value of recovered **3a** was only 2.6% (entry 1, Table 2), indicating very low enantioselectivity of the nitrile hydratase. This is in agreement with previous conclusion that there is a spacious pocket near the active site.[17,26] Noticeably, as indicated by the results compiled in Table 2, both biocatalytic efficiency and enantioselectivity of amide hydrolysis or overall reactions were strongly determined by the structures of the substrates. The replacement of phenyl group of **3a** (entry 2, Table 2) by benzyl led racemic 4-benzyl-2,3-allenenitrile **3b** (entry 3, Table 1) to undergo a much more rapid reaction than **3a** to produce almost quantitatively (a*R*)-(−)-amide **4b** and (a*S*)-(+)-acid **5b** in 80.6 and 84.2% ee values, respectively. Equally efficient reaction of racemic 4-(2-phenylethyl)-2,3-allenenitrile **3c** was also observed, and enantioselectivity was however only moderate (entry 4, Table 2). In sharp contrast to 4-benzyl-2,3-allenenitrile **3b** (entry 3, Table 2), 4-cyclohexylmethyl-2,3-allenenitrile **3d** took 44 h to furnish the corresponding amide and acid products in very low ee's (entry 5, Table 2). These results suggest a beneficial effect of a phenyl ring of 4-substituted 2,3-allenenitrile substrates on kinetic resolution catalyzed by *Rhodococcus erythropolis* AJ270. An optimally positioned phenyl substituent can result in both high reaction velocity and enantioselectivity. In addition to electronic effect, steric effect of the substrates was also vital to the amidase-catalyzed reaction. A stark contrast was evidenced by the biotransformations between 4-benzyl-2-methyl-2,3-allenenitrile **3e** and 4-methyl-4-phenyl-2,3-allenenitrile **3f**. While the former substrate remained almost intact after 5 days' interaction with biocatalyst, the later underwent effective biotransformations within 72 h to afford highly enantiopure allenamide (a*R*)-**4f** and allenoic acid (a*S*)-**5f** in good yields (entries 6 and 7, Table 2). The presence of methyl substituent at 2-position of 2,3-allenenitrile **3e** most probably increases the steric hindrance of cyano group, prohibiting therefore the accessibility of cyano group by the active site of the nitrile hydratase. In the case of **3f** and **4f**, methyl group at 4-position imposes probably little steric influence on the interaction between cyano or amido functional group and the nitrile hydratase or the amidase, respectively. Most strikingly, while 4-allyl-2,3-allenenitrile **3h** and 4-*n*-propyl-2,3-allenenitrile **3i** were hydrated very efficiently by the nitrile hydratase in a biphasic system, the amidase-catalyzed hydrolysis of resulting amides **4h** and **4i** was not observed at all. It was unexpected that the amidase did not function on substrate **4h**, as it was contrary to our previous observation that the amidase-catalyzed kinetic resolution is accelerated by the presence of a carbon−carbon unsaturated bond of amide substrates.[27]

The previous studies have concluded that the catalytic efficiency and enantioselectivity of the amidase within *Rhodococcus erythropolis* AJ270 cell are determined by the structures of different types of amides.[13,17−19] To a specific catalog of racemic amides of central chirality, dependence of biocatalysis on the nature of substituents has been observed.

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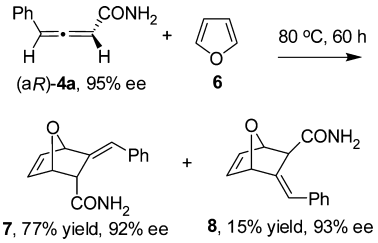
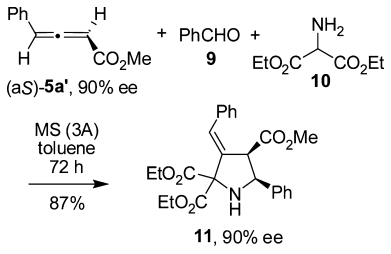
For example, the amidase-catalyzed kinetic resolution of 2-allyl-3-phenylpropanamide proceed more efficiently and enantioselectively than that of 3-phenyl-2-*n*-propylpropanamide, attributing to the presence of an unsaturated carbon−carbon bond binding domain of the amidase.[27] The unprecedented high *sensitivity* of the amidase toward the variation of a substituent and the substitution pattern of 2,3-allenamides **4** suggested a unique influence of axial chirality on biocatalysis. In other words, the interaction between perpendicular substituent(s) at γ-position to amido functional group of 2,3-allenamides and the active site of the amidase played a subtle but critical role in dictating catalytic efficiency and enantiocontrol. Although elucidation of detailed mechanism of enantioselective amidase awaits further study, the unusual profile of biotransformation of aforementioned axially chiral amides implies that the amidase may comprise most likely a relatively deep-buried and space-limited active site.

The resulting axially chiral allenes are conceivably important intermediates.[1−3] To demonstrate their utility in organic synthesis, cycloaddition reactions of enantioenriched (a*R*)-**4a** with furan and azomethine ylide were implemented. As illustrated in Scheme 2, Diels−Alder reaction between (a*R*)-**4a** with furan **6** proceeded effectively at 80 °C in a sealed tube to afford a mixture of *endo*-adduct **7** and *exo*-adduct **8** in the yield of 77 and 15%, respectively.[28] 1,3-Dipolar cycloaddition reaction of methyl 2,3-allenoate (a*S*)-**5a′** with azomethine ylide[29] that was formed in situ from the condensation between benzaldehyde **9** and amine **10** led to the formation of pyrrolidine product **11** in 87% yield as a single stereoisomer (Scheme 3). Illustrated in Scheme 4 is a further example of intramolecular cyclization reaction of 2,3-allenamide. In the presence of excess $CuBr_2$ under mild conditions, 2,3-allenamide (a*R*)-**4f** underwent bromolactamization reaction to furnish the formation of lactam **12**, which contains a tetrasubstituted carbon center. It is interesting to note that, as Ma and Xie[30] showed previously, intramolecular cyclization of racemic *N*-benzyl-4-methyl-4-phenyl-2,3-allenamide and *N*-benzyl-4,4-dimethyl-2,3-allenamide gave an iminolactone (resulting from the reaction of the oxygen of amide moiety as a nucleophile) and a lactam (resulting from the reaction of the nitrogen of amide as a nucleophile), respectively. Regioselective cyclization reactions was rationalized as the result of the steric hindrance of the 4,4-disubstituents at allenamides. In our case, however, no iminolactone product was observed at all. It appeared clearly that not only the substituents directly attaching to allene moiety but also the steric effect of *N*-substituent of amide would influence substantially the course of cyclization reactions. Remarkably, in all cases, axial chirality of allene reactants was fully transferred into or expressed as point chirality (stereogenic center) in the densely functionalized heterocyclic products, as the enantiomeric excess values of products were almost identical to that of the starting materials.

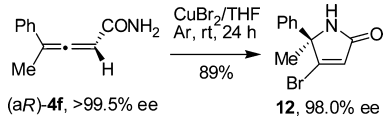
Scheme 2. Diels−Alder Reaction of (a*R*)-4a with Furan



Scheme 3. Synthesis of 11



Scheme 4. Bromolactamization of (*R*)-4f



CONCLUSION

In summary, we have shown *Rhodococcus erythropolis* AJ270, a nitrile hydratase-amidase containing microbial whole cell catalyst, is able to catalyze hydrolysis of racemic 2,3-allenenitriles in an aqueous phosphate buffer−*n*-hexane biphasic system. The method provides a unique approach to enantioenriched axially chiral 2,3-allenamides and 2,3-allenoic acids. The overall catalytic efficiency and enantioselectivity of biotransformations originated from a combination of an active but virtually nonenantioselective nitrile hydratase and a highly substrate-dependent enantioselective amidase. The resulting axially chiral allenes, which are not readily available by other means, are useful synthetic intermediates, and their applications are demonstrated by the constructions of densely functionalized heterocyclic compounds from cyclization and cycloaddition reactions in which the axial chirality of reactants was fully transferred into or expressed as point chirality of products.

EXPERIMENTAL SECTION

General Procedure for the Preparation of Racemic 2,3-Allenenitriles 3. To a solution of ylides **1** (10 mmol) in dry DCM (30 mL) at 0 °C was added dropwise a solution of triethylamine (11 mmol) in DCM (10 mL) while stirring. After the resulting mixture was stirred for 20 min, a solution of acyl chloride **2** (10 mmol) in DCM (10 mL) was added slowly through a dropping funnel during 20 min. The reaction mixture was kept stirring overnight at room temperature. DCM was removed using a rotary evaporator, and diethyl ether was then added to precipitate triphenylphosphine oxide. After filtration, the filtrate was concentrated and the residue was chromatographed on a silica gel column using a mixture of *n*-hexane and diethyl ether as mobile phase to afford pure products **3**.

4-Phenyl-2,3-allenenitrile ***3a.*** Colorless oil[31] (465 mg, 33%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H), 6.72 (d, J = 6.7 Hz, 1H), 5.67 (d, J = 6.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.8, 129.4, 129.1, 127.9, 112.5, 100.0, 71.3.

4-Benzyl-2,3-allenenitrile ***3b.*** Colorless oil (853 mg, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36−7.19 (m, 5H), 5.89 (dd, J = 13.9, 7.3 Hz, 1H), 5.22 (dd, J = 13.9, 2.9 Hz, 1H), 3.47 (dd, J = 7.3, 2.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 136.1, 127.3, 127.0, 125.6, 112.0, 95.2, 66.6, 32.3; IR (KBr) ν 3023, 2919, 2223, 1961, 1598, 1494 cm^{-1}; MS (EI) m/z (%) 156 $[M + 1]^+$ (10), 155 $[M]^+$ (100), 128 (80), 91 (83); HRMS (TOF-MS-EI) Anal. Calcd. for $C_{11}H_9N$ 155.0735 $[M]^+$, found 155.0737 $[M]^+$.

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4-(2-Phenylethyl)-2,3-allenenitrile ***3c***. Colorless oil (676 mg, 40%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.17 (m, 5H), 5.74 (dt, J = 15.1, 6.3 Hz, 1H), 5.18 (dt, J = 6.3, 3.1 Hz, 1H), 2.78 (t, J = 7.6 Hz, 2H), 2.50−2.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.2, 140.2, 128.6, 128.4, 126.4, 113.6, 96.1, 67.7, 34.6, 28.9; IR (KBr) ν 3022, 2927, 2223, 1959, 1494 cm^{-1}; MS (EI) m/z (%) 169 [M]$^+$ (18), 168 (55), 154 (30), 142 (60), 91 (100). Anal. Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.11; H, 6.60; N, 8.37.

4-(Cyclohexyl)methyl-2,3-allenenitrile ***3d***. Colorless oil (740 mg, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71−5.63 (m, 1H), 5.20−5.16 (m, 1H), 2.07−2.01 (m, 2H), 1.75−1.71 (m, 5H), 1.41−1.35 (m, 1H), 1.26−1.16 (m, 3H), 0.99−0.89 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 113.9, 95.3, 66.6, 37.5, 35.1, 32.9, 32.8, 26.3, 26.1; IR (KBr) ν 2925, 2852, 2225, 1959, 1445 cm^{-1}; MS (EI) m/z (%) 161 [M]$^+$ (6), 160 (4), 83 (100), 79 (73), 55 (60). Anal. Calcd for $C_{11}H_{15}N$: C, 81.94; H, 9.38; N, 8.69; Found: C, 82.11; H, 9.58; N, 8.66.

4-Benzyl-2-methyl-2,3-allenenitrile ***3e***. Colorless oil (507 mg, 30%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 − 7.18 (m, 5H), 5.73−5.72 (m, J = 7.2, 3.0 Hz, 1H), 3.43 (d, J = 7.2 Hz, 2H), 1.87 (d, J = 3.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.3, 138.0, 128.7, 128.4, 126.9, 116.2, 95.9, 34.3, 17.4; IR (KBr) ν 3029, 2924, 2219, 1958, 1598, 1495, 1445 cm^{-1}; MS (EI) m/z (%) 170 [M + H]$^+$ (10), 169 [M]$^+$ (78), 154 (75), 142 (38), 91 (100). Anal. Calcd for $C_{12}H_{11}N$: C, 85.17; H, 6.55; N, 8.28. Found: C, 85.37; H, 6.65; N, 8.24.

4-Methyl-4-phenyl-2,3-allenenitrile ***3f***. Colorless oil (481 mg, 31%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.32 (m, 5H), 5.54 (q, J = 3.0 Hz, 1H), 2.21 (d, J = 3.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 217.0, 132.7, 128.9, 128.7, 126.5, 113.3, 107.4, 69.0, 16.2; IR (KBr) ν 3000, 2222, 1946, 1492, 1448 cm^{-1}; MS (EI) m/z (%) 156 [M + H]$^+$ (10), 155 [M]$^+$ (100), 140 (65), 128 (28); HRMS (TOF-MS-EI) Anal. Calcd. for $C_{11}H_9N$ 155.0735 [M]$^+$, found 155.0737 [M]$^+$.

4-Benzyl-4-methyl-2,3-allenenitrile ***3g***. Colorless oil (253 mg, 15%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28−7.19 (m, 3H), 7.13−7.10 (m, 2H), 5.04−5.01 (m, 1H), 3.31 (s, 2H), 1.70 (d, J = 2.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.9, 136.9, 128.9, 128.6, 127.0, 114.1, 106.3, 66.4, 39.8, 17.3; IR (KBr) ν 2225, 1959 cm^{-1}; MS (EI) m/z (%) 169 [M]$^+$ (10), 168 (33), 142 (40), 91 (100); HRMS (TOF-MS-EI) Anal. Calcd. for $C_{12}H_{11}N$ 169.0891 [M]$^+$, found 169.0894 [M]$^+$.

4-Allyl-2,3-allenenitrile ***3h***. Colorless oil[32] (557 mg, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88−5.72 (m, 2H), 5.28−5.23 (m, 1H), 5.18−5.12 (m, 2H), 2.92−2.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 133.6, 117.4, 113.5, 95.3, 68.0, 31.4.

4-n-Propyl-2,3-allenenitrile ***3i***. Colorless oil[33] (482 mg, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75−5.68 (m, 1H), 5.23−5.19 (m, 1H), 2.17−2.08 (m, 2H), 1.54−1.44 (m, 2H), 0.96 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.3, 113.8, 96.7, 67.3, 29.3, 21.7, 13.5.

General Procedure for Biotransformations of Nitriles in a Biphasic System. In an Erlenmeyer flask (150 mL) with a screw cap a suspension of *Rhodococcus erythropolis* AJ270 cells[16] (2 g wet weight) in aqueous phosphate buffer (pH 7.0, 0.1 M, 50 mL) was activated at 30 °C for 0.5 h. A solution of nitriles **3** (1 mmol) in *n*-hexane (18 mL) and diethyl ether (2 mL) was then added in one portion, and the resulting biphasic mixture was incubated at 30 °C with orbital shaking (200 rpm). The reaction process was monitored using TLC method. After a period of time (see Table 2), the reaction was quenched by removing microbial cells through a Celite pad filtration. The filtration cake was washed consecutively by water (3 × 15 mL) and ethyl acetate (3 × 15 mL), and the organic phase of filtrate was separated and dried with anhydrous $MgSO_4$. The organic solvent was removed under a vacuum, and the residue was chromatographed on a silica gel column with a mixture of petroleum ether and ethyl acetate (2:1) and then pure ethyl acetate as the mobile phase to give pure 2,3-allenoic acids **5** and then 2,3-allenamides **4**. 2,3-Allenoic acids **5** were converted into their methyl esters **5′** upon the treatment with a solution of CH_2N_2 in diethyl ether at −10 °C for a couple of minutes.

Structures of all biotransformation products were established on the basis of their spectroscopic and microanalytic data. The absolute configurations of kinetically resolved products were assigned by comparison of the optical rotation of (a*S*)-**5a** and (a*S*)-**5f** with that of authentic samples reported in literature.[24] While the enantiomeric excess values of 2,3-allenamides **4** were measured directly using chiral HPLC analysis, all racemic 2,3-allenoic acids **5** were not resolved by chiral HPLC columns tested. To circumvent the problem, acids **5** were transformed into methyl esters **5′** by CH_2N_2, and their enantiomeric excess values were readily determined by means of chiral HPLC analysis. In practice, the enantiomeric excess values of amide products can be further increased easily by recrystallization. For example, recrystallization of (a*R*)-(−)-**4a** (94.8% ee) once from its acetone solution led to highly enantiopure **4a** with 97.6% ee.

(aR)-4-Phenyl-2,3-allenamide ***4a***. White solid (56 mg, 35%): mp 141−142 °C; $[\alpha]^{25}_D$ = −355.6° (c 0.45, $CHCl_3$; ee 94.8% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H), 6.64 (d, J = 6.4 Hz, 1H), 6.00 (d, J = 6.4 Hz, 1H), 5.82 (brs, 1H), 5.47 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.4, 166.2, 130.9, 129.1, 128.5, 127.4, 99.6, 94.4; IR (KBr) ν 3384, 3202, 1948, 1654, 1604, 1365 cm^{-1}. MS (EI) m/z (%) 159 [M]$^+$ (58), 141 (15), 116 (40), 115 (100). Anal. Calcd. for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.41; H, 5.76; N, 8.82.

(aR)-4-Benzyl-2,3-allenamide ***4b***. White solid (85 mg, 49%): mp 125−126 °C; $[\alpha]^{25}_D$ = −156.0° (c 0.3, $CHCl_3$); ee 80.6% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.22 (m, 5H), 5.84 (dd, J = 13.8, 7.3 Hz, 1H), 5.63 (brs, 1H), 5.60 (dd, J = 13.8, 2.6 Hz, 1H), 5.43 (brs, 1H), 3.48 (dd, J = 7.3, 2.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.9, 167.3, 138.6, 128.8, 128.4, 126.8, 96.3, 91.2, 34.4; IR (KBr) ν 3324, 3164, 1959, 1658, 1626, 1439, 1360 cm^{-1}. MS (EI) m/z (%) 173 [M]$^+$ (3), 172 (11), 156 (10), 129 (100), 91 (54). Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.22; H, 6.40; N, 8.02.

(aR)-4-(2-Phenyl)ethyl-2,3-allenamide ***4c***. White solid (84 mg, 45%): mp 104−105 °C; $[\alpha]^{25}_D$ = −57.5° (c 0.8, $CHCl_3$); ee 49.8% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.18 (m, 5H), 5.62−5.55 (m, 1H), 5.48−7.47 (m, 1H), 5.07−4.93 (m, 2H), 2.93−2.69 (m, 2H), 2.63−2.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.4, 167.4, 140.6, 128.7, 128.6, 126.3, 95.5, 90.7, 34.8, 29.6; IR (KBr) ν 3330, 3168, 2927, 1958, 1653, 1619, 1444 cm^{-1}. MS (EI) m/z (%) 187 [M]$^+$ (8), 186 (45), 144 (6), 129 (18), 91 (100). Anal. Calcd. for $C_{12}H_{13}NO$: C, 76.98; H, 7.00; N, 7.48. Found: C, 77.03; H, 6.93; N, 7.70.

(aR)-4-Cyclohexylmethyl-2,3-allenamide ***4d***. White solid (97 mg, 54%): mp 131−132 °C; $[\alpha]^{25}_D$ = −19.2° (c 0.85, $CHCl_3$); ee 5.8% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (brs, 1H), 5.63−5.56 (m, 1H), 5.54−5.53 (m, 1H), 5.45 (brs, 1H), 2.08−2.04 (m, 2H), 1.74−1.70 (m, 5H), 1.44−1.37 (m, 1H), 1.26−1.16 (m, 3H), 1.01−0. 93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.6, 167.7, 95.0, 90.1, 37.8, 35.8, 33.0, 26.3, 26.1; IR (KBr) ν 3334, 3173, 2921, 2847, 1959, 1656, 1616, 1446 cm^{-1}. MS (EI) m/z (%) 179 [M]$^+$ (3), 178 (5), 98 (40), 97 (67), 96 (100). Anal. Calcd. for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.49; H, 9.50; N, 7.72.

(aR)-4-Methyl-4-phenyl-2,3-allenamide ***4f***. White solid (68 mg, 39%): mp 144−145 °C; $[\alpha]^{25}_D$ = −298.7° (c 0.50, $CHCl_3$); ee >99.5% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44−7.29(m, 5H), 5.88 (q, J = 2.9 Hz, 1H), 5.76 (brs, 1H), 5.45 (brs, 1H), 2.24 (d, J = 2.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.5, 167.1, 133.9, 128.8, 128.1, 126.0, 106.3, 92.6, 16.3; IR (KBr) ν 3382, 3195, 1945, 1656, 1608, 1433 cm^{-1}; MS (EI) m/z (%) 173 [M]$^+$ (28), 128 (86), 115 (55), 44 (100). Anal. Calcd. for $C_{11}H_{11}NO$: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.14; H, 6.45; N, 8.20.

(aR)-4-Benzyl-4-methyl-2,3-allenamide ***4g***. White solid (79 mg, 42%): mp 131−132 °C; $[\alpha]^{25}_D$ = −68.4° (c 0.50, $CHCl_3$); ee 43.4% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.19 (m, 5H), 5.92 (brs, 1H), 5.66 (brs, 1H), 5.46 (s, 1H), 3.45−3.33 (m, 2H), 1.80 (t, J = 2.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.7, 168.4, 138.0, 128.8, 128.6, 126.9, 105.5, 89.9, 40.4, 17.8; IR (KBr) ν 3329, 3183, 1962, 1658, 1606, 1431 cm^{-1}; MS (ESI) m/z (%) 210 [M + Na]$^+$ (95), 188 [M + H]$^+$ (100); HRMS (FTMS-ESI) Anal. Calcd. for $C_{12}H_{13}NO$ 188.1070 [M + H]$^+$, found 188.1069 [M + H]$^+$.

(aR)-4-Allyl-2,3-allenamide ***4h***. White solid (112 mg, 91%): mp 91−92 °C; $[\alpha]^{25}_D$ = −1.5° (c 1.35, $CHCl_3$); ee 2.2% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90−5.58 (m, 5H), 5.18−5.09 (m, 2H), 5.13−5.11 (m, 1H), 2.94−2.88 (m, 2H); ^{13}C NMR (75

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MHz, $CDCl_3$) δ 208.7, 167.5, 134.7, 116.7, 94.8, 91.2, 32.0; IR (KBr) ν 3333, 3174, 1961, 1657, 1440 cm^{-1}; MS (EI) m/z (%) 123 $[M]^+$ (3), 122 (15), 106 (24), 79 (100). Anal. Calcd. for C_7H_9NO: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.15; H, 7.35; N, 11.41.

(aR)-4-n-Propyl-2,3-allenamide ***4i***. White solid[34] (113 mg, 90%): $[\alpha]^{25}_D$ = −1.4° (*c* 1.40, $CHCl_3$); ee 3.2% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 5.75 (brs, 1H), 5.68−5.62 (m, 1H), 5.57−5.55 (m, 1H), 5.28 (brs, 1H), 2.18−2.10 (m, 2H), 1.55−1.45 (m, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 208.5, 167.9, 96.4, 90.7, 29.9, 22.1, 13.6; IR (KBr) ν 3339, 3177, 2959, 1962, 1658, 1624, 1442 cm^{-1}; MS (EI) m/z (%) 125 $[M]^+$ (11), 124 (25), 108 (14), 96 (100), 67 (55). Anal. Calcd. for $C_7H_{11}NO$: C, 67.17; H, 8.86; N, 11.19. Found: C, 66.96; H, 8.93; N, 11.04.

(aS)-4-Phenyl-2,3-allenoic acid ***5a***. White solid[24,35] (59 mg, 37%): $[\alpha]^{25}_D$ = +368.5° (*c* 0.50, $CHCl_3$); ee 90.2% (chiral HPLC analysis of its methyl ester); ^1H NMR (300 MHz, $CDCl_3$) δ 11.20 (br, 1H), 7.35−7.25 (m, 5H), 6.69 (d, *J* = 6.3 Hz, 1H), 6.02 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.3, 171.0, 130.5, 129.0, 128.4, 127.6, 99.1, 91.5.

(aS)-4-Benzyl-2,3-allenoic acid ***5b***. Light yellow oil (85 mg, 49%): $[\alpha]^{25}_D$ = +61.5° (*c* 0.65, $CHCl_3$); ee 84.2% (chiral HPLC analysis of its methyl ester); ^1H NMR (300 MHz, $CDCl_3$) δ 7.35−7.24 (m, 5H), 5.84 (dd, *J* = 13.6, 7.4 Hz, 1H), 5.63 (dd, *J* = 13.6, 2.2 Hz, 1H), 3.50 (dd, *J* = 7.4, 2.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.1, 172.1, 138.3, 128.6, 128.6, 126.8, 95.3, 88.3, 34.0; IR (KBr) ν 3032, 2921, 2656, 2550, 1958, 1688, 1443 cm^{-1}; MS (EI) m/z (%) 174 $[M]^+$ (7), 157 (3), 129 (100), 91 (54); HRMS (TOF-MS-EI) Anal. Calcd. for $C_{11}H_{10}O_2$ 174.0681 $[M]^+$, found 174.0683 $[M]^+$.

(aS)-4-(2-Phenyl)ethyl-2,3-allenoic acid ***5c***. Light yellow oil (96 mg, 51%): $[\alpha]^{25}_D$ = +72.7° (*c* 0.55, $CHCl_3$); ee 49.0% (chiral HPLC analysis of its methyl ester); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.18 (m, 5H), 5.75−5.69 (m, 1H), 5.61−5.57 (m, 1H), 2.82−2.77 (m, 2H), 2.52−2.44 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.6, 171.5, 140.8, 128.5, 126.2, 95.1, 88.2, 34.9, 28.9; IR (KBr) ν 3027, 2925, 2657, 1957, 1687, 1443 cm^{-1}; MS (EI) m/z (%) 188 $[M]^+$ (8), 187 $[M-1]^+$ (15), 170 (36), 143 (55), 91 (100); HRMS (TOF-MS-EI) Anal. Calcd. for $C_{12}H_{12}O_2$ 188.0837 $[M]^+$, found 188.0835 $[M]^+$.

(aS)-4-Cyclohexylmethyl-2,3-allenoic acid ***5d***. Light yellow oil (79 mg, 44%): $[\alpha]^{25}_D$ = +21.1° (*c* 0.56, $CHCl_3$); ee 26.0% (chiral HPLC analysis of its methyl ester); ^1H NMR (300 MHz, $CDCl_3$) δ 5.67−5.59 (m, 1H),5.58−5.51 (m, 1H), 2.08−2.03 (m, 2H), 1.73−1.69 (m, 5H), 1.41−1.36 (m, 1H), 1.26−1.09 (m, 3H), 1.00−0.88 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.8, 172.1, 94.1, 87.1, 37.7, 35.2, 32.9, 32.8, 26.4, 26.1; IR (KBr) ν 3431, 2925, 2852, 1956, 1695,1443 cm^{-1}; MS (EI) m/z (%) 180 $[M]^+$ (3), 162 (5), 120 (22), 99 (95), 55 (100); HRMS (TOF-MS-EI) Anal. Calcd. for $C_{11}H_{16}O_2$ 180.1150 $[M]^+$, found 180.1152 $[M]^+$.

(aS)-4-Methyl-4-phenyl-2,3-allenoic acid ***5f***. White solid[24] (66 mg, 38%): $[\alpha]^{25}_D$ = +307.0° (*c* 0.48, $CHCl_3$); ee >99.5% (chiral HPLC analysis of its methyl ester); ^1H NMR (300 MHz, $CDCl_3$) δ 7.40−7.25 (m, 5H), 5.89 (q, *J* = 2.9 Hz, 1H), 2.22 (d, *J* = 2.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.5, 171.2, 133.8, 128.7, 128.1, 126.3, 106.0, 89.3, 16.1.

Methyl (aS)-4-phenyl-2,3-allenoate ***5a***′. Light yellow oil[21] (61 mg, 95%): $[\alpha]^{25}_D$ = +308.5° (*c* 0.65, $CHCl_3$); ee 90.2% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.24 (m, 5H), 6.63 (d, *J* = 6.4 Hz, 1H), 6.03 (d, *J* = 6.4 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 165.6, 131.0, 128.9, 128.2, 127.5, 98.7, 91.6, 52.3.

Methyl (aS)-4-benzyl-2,3-allenoate ***5b***′. Light yellow oil[36] (89 mg, 97%): $[\alpha]^{25}_D$ = +57.5° (*c* 0.83, $CHCl_3$); ee 84.2% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.21 (m, 5H), 5.81−5.74 (m, 1H), 5.66−5.61 (m, 1H), 3.75 (s, 3H), 3.50−3.47 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.9, 166.4, 138.6, 128.6, 128.5, 126.7, 94.9, 88.3, 52.1, 34.1.

Methyl (aS)-4-(2-phenyl)ethyl-2,3-allenoate ***5c***′. Light yellow oil (99 mg, 96%): $[\alpha]^{25}_D$ = +89.7° (*c* 0.85, $CHCl_3$); ee 49.0% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.32−7.26 (m, 2H), 7.25−7.19 (m, 3H), 5.70−5.63 (m, 1H), 5.62−5.58 (m, 1H), 3.72 (s, 3H), 2.81−2.76 (m, 2H), 2.50−2.42 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.4, 166.6, 140.9, 128.5, 128.4, 126.2, 94.8, 88.4, 52.1, 34.9, 29.1; IR (KBr) ν 3027, 2945, 1959, 1721, 1443, 1261 cm^{-1}; MS (EI) m/z (%) 202 $[M]^+$ (5), 201 (20), 170 (78), 143 (63), 91 (100). Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.19; H, 7.06.

Methyl (aS)-4-cyclohexylmethyl-2,3-allenoate ***5d***′. Light yellow oil (81 mg, 95%): $[\alpha]^{25}_D$ = +19.9° (*c* 0.60, $CHCl_3$); ee 26.0% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 5.61−5.55 (m, 2H), 3.73 (s, 3H), 2.06−2.01(m, 2H), 1.81−1.64 (m, 5H), 1.41−1.35 (m, 1H), 1.27−1.15 (m, 3H), 1.00−0.87 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.6, 166.8, 93.8, 87.2, 51.9, 37.7, 35.4, 32.9, 32.8, 26.4, 26.2; IR (KBr) ν 2925, 2851, 1958, 1723, 1442 cm^{-1}. MS (EI) m/z (%) 194 $[M]^+$ (3), 163 (7), 135 (12), 113 (100), 81 (41). Anal. Calcd. for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34. Found: C, 74.22; H, 9.41.

Methyl (aS)-4-methyl-4-phenyl-2,3-allenoate ***5f***′. Light yellow oil[37] (67 mg, 94%): $[\alpha]^{25}_D$ = +261.0° (*c* 0.50, $CHCl_3$); ee >99.5% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.24 (m, 5H), 5.90 (q, *J* = 2.9 Hz, 1H), 3.75 (s, 3H), 2.20 (d, *J* = 2.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.0, 166.2, 134.2, 128.6, 127.9, 126.2, 105.5, 89.5, 52.1, 16.2.

Methyl (aS)-4-benzyl-4-methyl-2,3-allenoate ***5g***′. Light yellow oil (101 mg, 50%): $[\alpha]^{25}_D$ = +33.5° (*c* 0.40, $CHCl_3$); ee 48.4% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.23 (m, 5H), 5.51 (m, 1H), 3.74 (s, 3H), 3.40 (s, 2H), 1.74 (d, *J* = 2.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.1, 166.9, 137.9, 129.0, 128.4, 126.7, 103.8, 86.7, 51.9, 40.1, 17.2; IR (KBr) ν 2948, 1964, 1720, 1443 cm^{-1}; MS (EI) m/z (%) 202 $[M]^+$ (4),, 170 (31), 143 (100), 91 (90); HRMS (TOF-MS-EI) Anal. Calcd. for $C_{13}H_{14}O_2$ 202.0994 $[M]^+$, found 202.0996 $[M]^+$.

Diels−Alder Reaction of (*R*)-4-Phenyl-2,3-allenamide 4a with Furan 6. A mixture of (a*R*)-**4a** (1 mmol, 159 mg) and furan **6** (10 mL) was sealed in a tube and was then stirred at 80 °C for 60 h. After removal of unreacted furan, the residue was chromatographed on a silica gel column eluted with a mixture of petrolum ether and ethyl acetate (1:1) to afford pure products **7** (175 mg, 77%) and **8** (34 mg, 15%). **7**: White solid; mp 160−162 °C; $[\alpha]^{25}_D$ = +206.7° (*c* 0.90, $CHCl_3$); ee 93.0% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.34−7.25 (m, 5H), 6.70−6.69 (m, 1H), 6.59 (d, *J* = 5.6 Hz, 1H), 6.45 (d, *J* = 5.6 Hz, 1H), 5.44 (d, *J* = 4.7 Hz, 1H), 5.26 (s, 1H), 5.20 (brs, 1H), 5.11 (brs, 1H), 4.02−4.00 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 136.2, 135.7, 134.8, 134.4, 128.7, 128.0, 124.5, 85.2, 81.4, 50.4; IR (KBr) ν 3409, 3175, 1666 cm^{-1}; MS (EI) m/z (%) 227 $[M]^+$ (5), 159 (52), 140 (50), 115 (100), 68 (68). Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.76; H, 5.98; N, 6.12.

8: White solid; mp 192−193 °C; $[\alpha]^{25}_D$ = −215.2° (*c* 0.45, $CHCl_3$); ee 92.0% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.31 (m, 4H), 7.26 − 7.24 (m, 1H), 6.67 (s, 1H), 6.53−6.46 (m, 2H), 6.02 (brs, 1H), 5.30−5.27 (m, 2H), 5.23 (brs, 1H), 3.29 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 135.9, 135.7, 135.4, 135.3, 128.7, 128.2, 128.0, 125.1, 84.0, 83.8, 50.8; IR (KBr) ν 3435, 3203, 1631 cm^{-1}; MS (EI) m/z (%) 227 $[M]^+$ (9), 155 (40), 140 (83), 115 (80), 68 (100). Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.72; H, 5.90; N, 5.88.

Reaction of Methyl (*S*)-4-Phenyl-2,3-allenoate 5a′ with Benzaldehyde 9 and Amine 10. To a well stirred mixture of benzaldehyde (1.1 mmol, 117 mg), *p*-toluenesulfonic acid (0.15 mmol, 26 mg), molecular sieve (3 Å, 1 g) and methyl (a*S*)-4-phenyl-2,3-allenoate **5a**′ (1 mmol, 174 mg) in toluene (5 mL) was added a solution of amine **10** (1 mmol, 175 mg) in toluene (5 mL) at room temperature. The resulting reaction mixture was stirred at ambient temperature for another 3 days. Molecular sieves were removed by filtration, and the filtration cake was washed with ethyl acetate. The combined filtrate was mixed with a saturated aqueous solution of $NaHCO_3$ (50 mL). After separation, aqueous phase was extracted with ethyl acetate (2 × 30 mL), and combined organic solution was dried with anhydrous $MgSO_4$. Organic solvent was removed using a rotary evaporator, and the residue was chromatographed on a silica gel column eluted with a mixture of petrolum ether and ethyl acetate (15:1) to afford pure product **11** (380 mg, 87%): White solid; mp 86−

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87 °C; $[\alpha]^{25}_{D}$ = +26.6° (*c* 0.58, $CHCl_3$); ee 90.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40−7.26 (m, 10H), 7.06 (s, 1H), 4.79 (d, *J* = 6.5 Hz, 1H), 4.39−4.28 (m, 4H), 4.03 (d, *J* = 6.5, 1H), 3.28 (s, 3H), 1.37−1.31 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 170.8, 168.5, 137.4, 136.1, 136.1, 131.4, 128.7, 128.6, 128.3, 127.9, 126.6, 76.0, 64.9, 62.3, 62.2, 54.8, 51.6, 14.1; IR (KBr) ν 3348, 2927, 1738, 1444 cm^{-1}; MS (ESI) *m*/*z* (%) 460 $[M + Na]^+$ (90), 438 $[M + H]^+$ (100); HRMS (FT-ICRMS) Anal. Calcd. for $C_{25}H_{27}NO_6$ 438.1911 $[M + H]^+$, found 438.1912 $[M + H]^+$.

Conversion of (*R*)-4-Methyl-4-phenyl-2,3-allenamide 4f into Lactam 12. Under argon protection, a mixture of (a*R*)-**4f** (1 mmol, 173 mg) and $CuBr_2$ (4 mmol) in dry THF (10 mL) was stirred at room temperature for 24 h. After removal of THF, an aqueous solution of NaOH (1 M, 20 mL) was added. Copper salts were removed by filtration through a Celite pad, and the filtration cake was washed with ethyl acetate. The filtrate was extracted with diethyl ether, and combined organic phase was dried over anhydrous $MgSO_4$. Organic solvents were evaporated, and the residue was chromatographed on a silca gel column. Elution with a mixture of petrolum ether and ethyl acetate (1:1) gave pure **12** (224 mg, 89%): Light yellow oil; $[\alpha]^{25}_{D}$ = −137.5° (*c* 0.75, $CHCl_3$); ee 98.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (m, 5H), 6.37 (s, 1H), 1.91 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.90, 156.91, 136.4, 129.2, 128.8, 125.6, 120.6, 90.5, 23.7; IR (KBr) ν 1673 cm^{-1}; MS (ESI) *m*/*z* (%) 252 $[M + H]^+$ (100), 254 $[M + H]^+$ (96); HRMS (FT-MS-ESI) Anal. Calcd. for $C_{11}H_{10}BrNO$ 252.0019 $[M + H]^+$, found 252.0016 $[M + H]^+$.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of products, HPLC chromatograms of products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangmx@mail.tsinghua.edu.cn.

Notes

The authors declare no competing financial interest.

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