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Nitrile biotransformations for the practical synthesis of highly enantiopure azido carboxylic acids and amides, 'click' to functionalized chiral triazoles and chiral β-amino acids

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Abstract—Under very mild conditions, biotransformations of racemic azido nitriles using *Rhodococcus erythropolis* AJ270, a nitrile hydratase/amidase-containing microbial whole-cell catalyst, afforded highly enantiopure, (*R*)-α-arylmethyl- and (+)-α-cyclohexylmethyl-β-azidopropanoic acids and their (*S*)- and (−)-carboxamide derivatives in excellent yields. The resulting functionalized chiral organoazides were converted in a straightforward fashion to a pair of antipodes of α-benzyl-β-amino acids (*R*)-**13** and (*S*)-**13**. Azido carboxamide (*S*)-**11a** and azido carboxylic acid (*R*)-**12a** underwent 'click' reactions with diethyl acetylenedicarboxylate and phenylacetylene to produce functionalized chiral triazoles **14** and **15**, respectively. The easy preparation of the starting nitrile substrates, highly efficient and enantioselective biotransformation reactions, and versatile utility of the resulting functionalized azido carboxylic acids and amide derivatives, render this method very attractive and practical in organic synthesis.

1. Introduction

There has been an increasing interest in organoazide compounds since the advent of highly efficient, regiospecific, and catalytic cycloaddition reactions of azides with terminal acetylenes.[1] In addition to their wide applications in 'click' synthesis,[1–3] organoazides have been known for a long time as useful and versatile intermediates in organic synthesis.[4] For example, organoazides are powerful 1,3-dipole components, which are able to react with a variety of activated alkenes and alkynes, and other 1,3-dipolarophiles to form five-membered heterocycles.[5] They also act as the masked amines,[4e,6] the source of nitrenes[4e,7] and aza ylides,[4e,8] in addition to the well-known Curtius rearrangement and related reactions. Despite the availability of preparative methods for organic azides,[4] chiral organoazides are mainly obtained from diastereoselective reactions of an azide ion with chiral substrates.[4e] The synthesis of enantiopure organoazides through catalytic enantioselective reactions is largely unexplored and still remains as a challenge for synthetic chemists.[9] To meet the ever increasing demand for 'click' chemistry in the study of life science[2] and materials science,[3] exploration of efficient, and practical synthesis of highly enantiopure chiral organoazide entities, particularly functionalized and transformable ones, is of great importance.

Biotransformations of nitriles, either through direct conversion from a nitrile to a carboxylic acid catalyzed by a nitrilase,[10] or through the nitrile hydratase-catalyzed hydration of a nitrile followed by amide hydrolysis catalyzed by the amidase,[11] are effective and environmentally friendly methods for the production of carboxylic acids and their amide derivatives.[12] Recent studies have shown that biotransformations of nitriles complement the existing asymmetric chemical and enzymatic methods for the synthesis of chiral carboxylic acids and their derivatives.[13,14] The distinct features of enzymatic transformations of nitriles are the formation of enantiopure carboxylic acids, and the straightforward generation of enantiopure amides, which are valuable organonitrogen compounds in synthetic chemistry. Recently, we[13c] have shown that *Rhodococcus erythropolis* AJ270,[15] a nitrile hydratase/amidase-containing whole-cell catalyst, is able to efficiently and enantioselectively transform functionalized nitriles, including aminonitriles,[16] allyl-substituted arylacetonitriles,[17] cyclo-

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propanecarbonitriles,[18] and oxiranecarbonitriles,[19] into the corresponding chiral carboxylic acids and amides. The intention of further exploring the synthetic applications of the powerful *R. erythropolis* AJ270 whole-cell catalyst in organic chemistry led us to the current study. Considering the electronic and steric effects of the azido group and its compatibility with living systems,[2] we envisaged that the biotransformations of azido nitriles might offer us a novel approach to optically active azido acid and amide derivatives. It is also interesting to look at the influence of azido group on the reaction efficiency and enantioselectivity of the nitrile hydratase and the amidase. Herein, we report an efficient biocatalytic hydrolysis of nitriles for the practical preparation of highly enantiomerically pure α-arylmethyl-β-azido propanoic acids and amide derivatives. The synthetic utility of the resulting chiral azides will also be demonstrated in the click synthesis of triazole-containing chiral carboxylic acids and amides, and in the synthesis of usual α-branched β-amino acids.

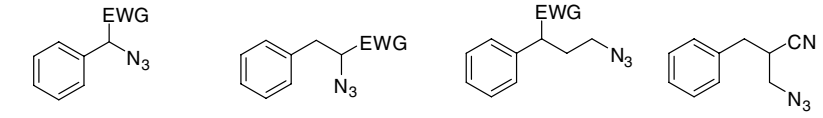
2. Results and discussion

No biotransformations of nitriles bearing an azido substituent have been reported in the literature until now. Interestingly, however, Meldal et al. have observed that, in the presence of *Pseudomonas putida* L-aminopeptidase-containing *E. coli* cells, α-azidophenylacetamide underwent dynamic kinetic resolution to yield optically active (*S*)-α-azidophenylacetic acid.[20] To start our investigation, we first examined the *R. erythropolis* AJ270 whole-cell catalyzed hydrolysis of α-azidophenylacetonitrile **1**. Under conventional conditions for the nitrile biotransformation reaction,[16] azido nitrile **1** underwent a highly efficient hydration reaction to afford optically active amide (−)-**2** and (+)-**1** in good yield, albeit with low enantioselectivity (Table 1, entry 1). Biohydrolysis of α-azidophenylacetamide with the amidase in *R. erythropolis* AJ270 was ineffective, and no corresponding α-azidophenylacetic acid **3** was observed. It was also found that α-azidophenylacetamide **2** was unstable under the incubation conditions, undergoing slow decomposition to form 2-oxophenylacetamide (Table 1, entry 2). We then tried azido nitrile substrates **4**, **7**, and **10a** in which methylene(s) were introduced inbetween the stereogenic center and benzene ring (**7** and **10a**) or inbetween the stereogenic center and azido group (**4** and **10a**). All these substrates and their corresponding amides and acids turned out to be stable under the reaction conditions. Catalyzed by *R. erythropolis* AJ270 whole cells, both nitriles **4** and **7** were readily hydrated. However, the sequential biocatalytic hydrolyses of amides **5** and **8** differed remarkably. While 50% conversion of amide **5** into acid **6** was achieved within several hours, some took a week to transform half of the amide **8** into acid **9** (Table 1, entries 3–6). Unfortunately, in all cases, the enantioselectivity for both nitrile hydration and amide hydrolysis reactions was unsatisfactory and, therefore, the method was not a practical way to prepare azido acids **6** and **9** and amides **5** and **8** with high enantiomeric purity.

In sharp contrast to substrates **4** and **7**, α-benzyl-β-azidopropionitrile **10a** appeared as an excellent substrate towards the *R. erythropolis* AJ270 whole-cell catalyst. Thus, biotransformations of racemic nitrile **10a** proceeded efficiently in a short period of time to furnish almost quantitative yields of (*S*)-azido amide **11a** and (*R*)-azido acid **12a** with excellent enantiomeric excesses (Table 1, entry 8). It should be noted that the overall high enantioselectivity of the nitrile biotransformations originates from the combined effect of enantioselective amidase and nitrile hydratase, with the former playing a dominant role, since the enantiomeric excess of the recovered nitrile (*S*)-**10a** is low (Table 1, entry 7).

To examine the scope of the reaction and influence of the substituent on the efficiency and enantioselectivity of biotransformations, a number of racemic α-arylmethyl-β-azidopropionitriles **10b–h** were prepared and subjected to

Table 1. Biotransformations of racemic azido nitriles



(±)-**1** (EWG = CN)
(-)-**2** (EWG = $CONH_2$)
3 (EWG = CO_2H)

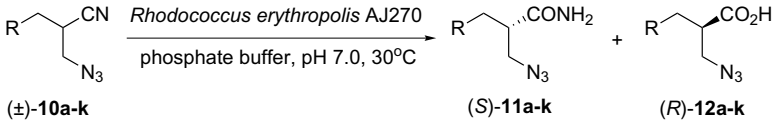
(±)-**4** (EWG = $CONH_2$)
(-)-**5** (EWG = $CONH_2$)
(-)-**6** (EWG = CO_2H)

(±)-**7** (EWG = CN)
(-)-**8** (EWG = $CONH_2$)
(+)-**9** (EWG = CO_2H)

(±)-**10a**

Entry	Nitrile (mmol)	Reaction time[a]	Nitrile recovered yield[b] (%), ee[c] (%)	Amide yield[b] (%), ee[c] (%)	Acid yield[b] (%), ee[c] (%)
1	**1** (2.0)	10 min	(+)-**1** (51), (29.4)	(−)-**2** (45), (64.5)	—
2	**1** (0.5)	3 d	—	(−)-**2** (38), (5.1)	—[d]
3	**4** (2.0)	1.5 h	(−)-**4** (47), (15.8)	(−)-**5** (44), (21.8)	
4	**4** (0.5)	6 h	—	(−)-**5** (54), (36.6)	(−)-**6** (45), (45.0)
5	**7** (2.0)	15 min	(+)-**7** (40), (70.8)	(+)-**8** (58), (56.4)	—
6	**7** (0.5)	7 d	—	(−)-**8** (41), (48.4)	(+)-**9** (37), (80.0)
7	**10a** (2.0)	10 min	(*S*)-**10a** (54), (15.8)	(*R*)-**11a** (36), (11.8)	—
8	**10a** (2.0)	3.5 h	—	(*S*)-**11a** (48), (>99.5)	(*R*)-**12a** (49), (96.2)

[a] Biotransformation was carried out in a suspension of *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in phosphate buffer (50 ml, pH 7.0) at 30 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral column (SI).
[d] 2-Oxophenylacetamide (19%) was isolated.



(±)-**10a-k** (*S*)-**11a-k** (*R*)-**12a-k**

Scheme 1. Enantioselective biotransformations of racemic α-substituted β-azidopropionitriles.

incubation with *R. erythropolis* AJ270 (Scheme 1). As illustrated in Table 2, except for nitriles bearing a *p*-bromophenyl **10h** (Table 2, entry 9), a *m*-chlorophenyl **10f** (Table 2, entry 6) or an *o*-chlorophenyl substituent **10g** (Table 2, entry 8), all substrates underwent complete hydration and ca. 50% amide hydrolysis within 5 h. By halving the concentration of the substrates **10f** and **10h**, rapid biotransformations were all effected (Table 2, entries 7 and 10). Although the nature of the substituent and its substitution pattern on the benzene ring of the substrates **10a**–**h** played a part in determining the overall conversion rate, they did not seem to influence the enantioselectivity of the biotransformations. In all cases of the α-arylmethyl-β-azidopropionitriles **10b**–**h**, biotransformations yielded highly enantiopure (*R*)-acid and (*S*)-amide products.

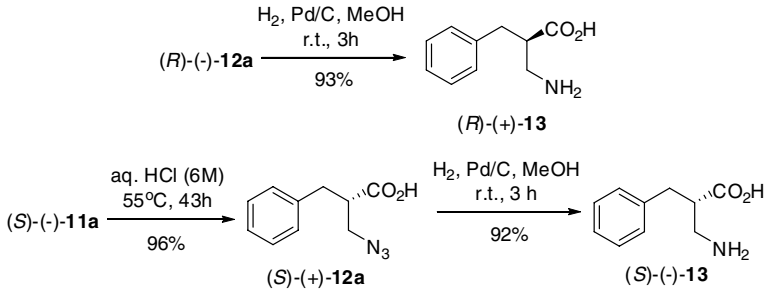
Encouraged by these results, we next studied the biotransformations of racemic β-azidopropionitriles **10i**–**k** that contain an α-alkyl group. Although the conversion of the alkyl-substituted nitriles **10i**–**k** was almost comparable to that of aryl-substituted substrates, the replacement of an aryl group by an alkyl moiety gave rise to a dramatic change in the enantiocontrol. While the reaction of α-cyclohexylmethyl-β-azidopropionitrile **10i** afforded equally excellent enantiomeric yields of the products as that of biotransformations of α-phenylmethyl-β-azidopropionitrile **10a**, only moderate enantioselectivities could be obtained for the biotransformations of α-cyclopropylmethyl- and α-propyl-β-azidopropionitriles **10j** and **10k** (Table 2, entries 11–13).

The aforementioned outcome, along with our previous studies,[13c] showed that the nitrile hydratase involved in *R. erythropolis* AJ270 is generally less enantioselective against most of the racemic nitriles, whereas the amidase exhibits good to excellent enantioselectivity. In most cases, the nitrile hydratase was not sensitive to the structural variations of the nitrile substrates, that is, the nitrile hydratase catalyzes efficient hydration of many nitriles with low to moderate enantioselectivity. This observation is in agreement with the structure of the nitrile hydratase enzyme, which contains a spacious active site.[21] The action of the amidase, on the other hand, is highly dependent upon the structure, particularly the steric features of the amide substrates used. This has been shown clearly by the fact that the biotransformations of α-azido-β-phenylpropionitrile **4**, α-benzyl-β-azidopropionitrile **10a**, and α-cyclopropylmethyl-β-azidopropionitrile **10j** resulted in large differences in enantiocontrol (Table 1, entry 4; Table 2, entries 1 and 12). This suggests that the presence of both an aryl unit or a six-membered cyclohexyl moiety and a methylene segment between the azido group and the stereogenic center in the structure is crucial for obtaining excellent enantioselectivity. It is worth noting that the azido group must also have played a very intriguing role in biocatalytic reactions, as racemic α-benzylpentanenitrile underwent sluggish biotransformations (4 days) to afford nearly quantitative yields of the corresponding amide and acid products but with 66.5% and 52.8% enantiomeric excess values, respectively. To rationalize the beneficial azido effect is difficult at this stage because of lack of structural information of

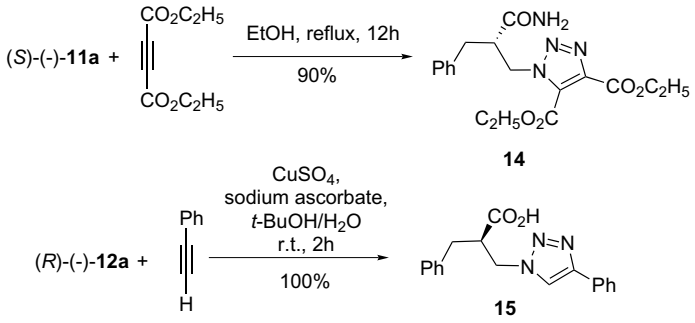
Table 2. Enantioselective biotransformations of racemic α-substituted β-azidopropionitriles

Entry	**10**	R	Reaction conditions[a]	**11** Yield[b] (%)	**11** ee[c] (%)	**12** Yield[b] (%)	**12** ee[c] (%)
1	**10a**	C_6H_5	2 mmol, 3.5 h	48	>99.5	49	96.2
2	**10b**	4-MeO–C_6H_5	2 mmol, 1 h	47	>99.5	48	94.0
3	**10c**	4-Me–C_6H_5	2 mmol, 4.5 h	48	97.2	49	>99.5
4	**10d**	4-F–C_6H_5	2 mmol, 4 h	48	>99.5	47	>99.5
5	**10e**	4-Cl–C_6H_5	2 mmol, 3.5 h	48.5	86.7	44	93.2
6	**10f**	3-Cl–C_6H_5	2 mmol, 24 h	54	81.2	40	>99.5
7	**10f**	3-Cl–C_6H_5	1 mmol, 6 h	50	>99.5	47	94.8
8	**10g**	2-Cl–C_6H_5	2 mmol, 20.5 h	48.5	97.3	48	>99.5
9	**10h**	4-Br–C_6H_5	2 mmol, 4.5 h[d]	41.5	93.5	40	95.3
10	**10h**	4-Br–C_6H_5	1 mmol, 2 h	47	>99.5	46.5	93.6
11	**10i**	C_6H_{11}	2 mmol, 7 h	49	>99.5	49	95.5[e]
12	**10j**	C_3H_5	2 mmol, 1.75 h	41	83.0	58	58.6[e]
13	**10k**	C_2H_5	2 mmol, 1.5 h	48	84.6	48	73.5[e]
14	**10a**	C_6H_5	12 mmol, 5 h[f]	48	>99.5	51	97.4

[a] The biotransformation was carried out in a suspension of *Rhodococcus erythropolis* AJ270 cells (2 g wet weight) in a phosphate buffer (50 ml, pH 7.0) at 30 °C.
[b] Isolated yield.
[c] Determined by HPLC analysis using a chiral column (see SI).
[d] Nitrile **10h** (~20%) was recovered.
[e] Enantiomeric excess was determined on its corresponding benzyl ester using HPLC analysis with a chiral column (see SI).
[f] A suspension of *Rhodococcus erythropolis* AJ270 cells (12 g wet weight) in 300 ml of phosphate buffer was used.



Scheme 2. Preparation of enantiomerically pure α-benzyl-β-aminopropanoic acid (*R*)-(+)-**13** and its antipode (*S*)-(−)-**13**.



Scheme 3. Click reactions of chiral azido amide and azido acid.

the amidase. This might be most probably due to the unique structure and affinity of the azido moiety that facilitates its binding and recognition to the active site of the enzyme.

To show the practical usefulness of this microbial catalytic process, a multigram scale biotransformation of azido nitrile **10a** (12 mmol) was carried out in a suspension of *R. erythropolis* AJ270 (12 g wet weight) in 300 ml of phosphate buffer. After 5 h of incubation, highly enantiomerically pure (*S*)-(−)-amide **11a** and (*R*)-(−)-acid **12a** were both obtained in more than a gram quantity (Table 2, entry 14). To demonstrate the synthetic applications of chiral azido products, and also in order to examine the stereochemistry of biotransformations, both amide **11a** and acid **12a** were transformed into β-amino acids. Thus, the catalytic hydrogenation of acid **12a** under very mild conditions afforded (*R*)-(+)-α-benzyl-β-aminopropanoic acid (*R*)-(+)-**13** in 93%, while its antipode (*S*)-(−)-**13** was readily produced from chemical hydrolysis of (*S*)-(−)-amide **11a**, which gave azido acid (*S*)-(+)-**12a**, followed by catalytic hydrogenation (Scheme 2). No racemarization was observed during the chemical hydrolysis and hydrogenation processes. The absolute configurations of the β-amino acids (*R*)-(+)-**13** and (*S*)-(−)-**13**, that were assigned, based on the comparison of the sign of the specific rotation with that of authentic samples,[22] indicate that the biotransformation products, azido amide (−)-**11a** and azido acid (−)-**12a** are (*S*)- and (*R*)-configured, respectively. The amidase involved in *R. erythropolis* AJ270, therefore, is (*R*)-enantioselective against substrates **12a**. Chiral β-amino acids are very important building blocks in the synthesis of β-lactam antibiotics and β-peptide mimics.[23] The synthesis of highly enantiopure α-branched β-amino acids, or β^2-amino acids as proposed by Seebach,[24] has mainly relied on diastereoselective syntheses utilizing various chiral auxiliaries.[23] This has been demonstrated by Seebach[24] and Juaristi.[22,25] Biotransformations of azido nitriles, coupled with chemical hydrolysis, provide a practical, straightforward and environmentally benign approach to the synthesis of highly enantiomerically pure α-branched β-amino acids in both antipodal forms.

The synthetic potential of enantiopure azido acids and their amide derivatives resulting from biotransformations of nitriles has been further demonstrated by the preparation of functionalized chiral triazole compounds. Scheme 3 shows the convenient and high yielding formation of **14** from a 1,3-cycloaddition reaction of (*S*)-(−)-**11a** with diethyl acetylenedicarboxylate in refluxing ethanol. Following the Sharpless method,[1b] azido acid (*R*)-(−)-**12a** was efficiently clicked to phenylacetylene to afford triazole-containing chiral carboxylic acid **15** in quantitative yield.

3. Conclusion

In conclusion, we have shown that *R. erythropolis* AJ270 whole cells can catalyze the hydrolysis of a number of azido nitriles under very mild conditions. Both the efficiency and enantioselectivity of biocatalysis, however, were strongly dependent upon the structures of both nitrile and amide substrates. While almost all the azido nitriles were efficiently hydrated with the aid of low enantioselective nitrile hydratase, the amidase exhibited excellent enantioselectivity against (*R*)-α-arylmethyl- and (+)-α-cyclohexylmethyl-β-azidopropanamides. The biocatalytic reaction of racemic

azido nitriles has provided a highly efficient and practical synthesis of highly enantiopure (*R*)-α-arylmethyl- or (+)-α-cyclohexylmethyl-β-azidopropanoic acids, and their corresponding (*S*)- or (−)-amide derivatives. The resulting functionalized chiral organoazides, which are difficult to prepare using other methods, can serve as useful intermediates in the synthesis of polyfunctionalized chiral molecules. This has been exemplified by the straightforward synthesis of a pair of antipodes of α-benzyl-β-amino acids through facile hydrogenation and chemical hydrolysis. Azido carboxamide (*S*)-**11a** and azido carboxylic acid (*R*)-**12a** have been further demonstrated as reactive species, which readily undergo click chemistry with diethyl acetylenedicarboxylate and phenylacetylene to produce functionalized chiral triazoles **14** and **15**, respectively. The easy preparation of the starting nitrile substrates, highly efficient and enantioselective biotransformation reactions, and the versatile utility of the resulting azido carboxylic acids and amide derivatives render this method very attractive and practical in organic synthesis. The extension of biotransformations for the synthesis of various chiral azides and their applications in organic synthesis are actively being investigated in this laboratory.

4. Experimental

4.1. Preparation of starting nitriles and their spectroscopic data

4.1.1. Preparation of racemic α-azidophenylacetonitrile 1. To a mixture of racemic α-azidophenylacetic acid[1] (4.425 g, 25 mmol) in dry THF (70 ml) at −25 °C was added triethylamine (3.5 ml, 25 mmol) under a nitrogen atmosphere. After stirring for 5 min, ethyl chlorocarbonate (2.4 ml) was added and the resulting mixture was stirred for another 15 min. Dry ammonia gas was then bubbled through the mixture for 45 min. The cooling bath was removed and the mixture was stirred at ambient temperature to allow the temperature of the mixture to increase to 0 °C. The reaction mixture was mixed with water (100 ml) and extracted with diethyl ether (3 × 70 ml). After drying over anhydrous $MgSO_4$ and removal of the solvent, the residue was crystallized in a mixture of dichloromethane and petroleum ether at −75 °C to give α-azidophenylacetoamide **2** (1.82 g, 39%). To a solution of **2** (500 mg, 2.84 mmol) in dry DMF (60 ml) at 0 °C was added $SOCl_2$ (0.31 ml). After stirring for 25 min, ice water (60 ml) was added and the mixture was extracted with diethyl ether (3 × 30 ml). The organic layer was dried over with anhydrous $MgSO_4$ and the solvent removed under vacuum. Column chromatography using silica gel eluted with a mixture of petroleum ether and ethyl acetate (30:1) gave α-azidophenylacetonitrile **1**[2] (365 mg, 81%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (5H, s), 5.23 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.0, 130.5, 129.6, 127.4, 115.5, 54.4 ppm; IR (KBr) ν 2111 cm^{-1} (–N_3).

4.1.2. Preparation of α-azido-β-phenylpropionitrile 4. α-Bromo-β-phenylpropanamide[3] (1.824 g) was dissolved in DMSO (12 ml) and a solution of sodium azide in DMSO (17.6 ml, 0.5 M) was added. The mixture was stirred at room temperature for 5 h. Water (150 ml) was added and the resulting mixture was extracted with diethyl ether (3 × 50 ml). After removal of the solvent, the oil residue was stirred with water (25 ml) at 50 °C to give α-azido-β-phenylpropanamide **5** as a precipitate (1.925 g, 84%). Following the same procedure for the preparation of **1**, **5** was converted into α-azido-β-phenylpropionitrile **4** in 71.0% yield: oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45–7.24 (5H, m), 4.34 (1H, t, $J = 7.1$ Hz), 3.10 (1H, d, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.5, 129.4, 129.0, 128.2, 115.8, 52.5, 39.1 ppm; IR (KBr) ν 2110 (N_3) cm^{-1}; MS (EI) m/z (%) 172 (1) [M]$^+$, 144 (2), 130 (2), 117 (31), 91 (100). Anal. Calcd for $C_9H_8N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.66; H, 4.61; N, 32.79.

4.1.3. Preparation of 4-azido-2-phenylbutyronitrile 7. Under a nitrogen atmosphere, 4-hydroxy-2-phenyl-butyronitrile[4] (1.61 g, 10 mmol) was dissolved in dry THF (100 ml), and triphenyl phosphine (2.88 g, 11 mmol) and hydrazoic acid solution in toluene (1.6 N, 15 ml) were added while stirring at room temperature. Diisopropyl azodicarboxylate (11 mmol) was added dropwise and then the mixture was kept for stirring for 30 min. Water (50 ml) was added into the reaction mixture, and THF removed under vacuum. After extraction with diethyl ether (3 × 50 ml), the combined organic layer was concentrated to 20 ml after which petroleum ether (20 ml) was added to precipitate triphenyl phospine oxide. The solvent was removed and the residue subjected to chromatography using a silica gel column eluted with a mixture of petroleum ether and ethyl acetate (10:1). 4-Azido-2-phenylbutyronitrile **7** (1.656 g, 89%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41–7.33 (5H, m), 3.97 (1H, dd, $J = 6.9$, 8.4 Hz), 3.57–3.48 (1H, m), 3.44–3.36 (1H, m), 2.21–2.07 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 129.4, 128.5, 127.4, 120.0, 48.2, 34.9, 34.3 ppm; IR (KBr) ν 2242 (CN), 2102 (N_3) cm^{-1}; MS (EI) m/z (%) 158 (22) [M–28]$^+$, 157 (43), 156 (59), 155 (100), 130 (47), 129 (84), 104 (72), 103 (56), 102 (30). Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.90; H, 5.35; N, 30.12.

4.1.4. Preparation of β-azido-α-benzylpropionitrile 10a. To a suspension of methyl 2-cyano-3-phenyl acrylate[5] (11.2 g, 60 mmol) in isopropanol (180 ml) cooled in a water bath was added sodium borohydride (6.84 g) with the resulting mixture stirred overnight at ambient temperature. Acetic acid (30%) was carefully added to the reaction mixture to quench the remaining sodium borohydride until no bubbling was observed. 2-Propanol was then removed under vacuum and the residue basified to pH 10 with aqueous sodium hydroxide (1 M) and extracted with diethyl ether (3 × 50 ml). After drying over with anhydrous $MgSO_4$ and removal of solvent, α-benzyl-β-hydroxypropionitrile (9.44 g, 98%) was isolated as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.24 (5H, m), 3.77 (2H, s), 2.97 (3H, s), 2.29 (1H, br); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.4, 129.0, 128.9, 127.4, 120.5, 61.8, 36.8, 34.5 ppm; IR (KBr) ν 3450 (OH), 2245 cm^{-1} (C≡O). Under a nitrogen atmosphere, α-benzyl-β-hydroxypropionitrile (805 mg, 5 mmol) was dissolved in dry THF (50 ml), and triphenyl phosphine (1.57 g, 6 mmol) and hydrazoic acid solution in toluene (1.6 M, 3 ml) were added. After cooling down

to 5 °C, diisopropyl azodicarboxylate (6 mmol) was added dropwise within 45 s and then stirred for another 30 s. Water (50 ml) was then added to the reaction mixture, and THF was removed under vacuum. The mixture was extracted with diethyl ether (3 × 40 ml) and the combined diethyl ether solution was concentrated to 10 ml. The addition of petroleum ether (10 ml) resulted in the precipitation of triphenyl phospine oxide. After removal of solvent and a silica gel column chromatography eluting with a mixture of petroleum ether and ethyl acetate (10:1), β-azido-α-benzylpropionitrile **10a** (441 mg, 47%) was obtained as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36–7.23 (5H, m), 3.54–3.47 (2H, m), 3.03–2.94 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 129.1, 129.0, 127.7, 119.4, 50.9, 35.4, 33.9 ppm; IR (KBr) ν 2244 (CN), 2108 (N_3) cm^{-1}; MS (EI) m/z (%) 158 (100) $[M-28]^+$, 157 (62), 140 (21), 130 (63), 105 (19), 91 (43). Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.55; H, 5.26; N, 30.40.

4.1.5. Nitriles 10b–k were prepared following the same procedure reported for the preparation of 10a

4.1.5.1. β-Azido-α-(*p*-methoxyphenylmethyl)propionitrile 10b. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (2H, d, $J = 8.7$ Hz), 6.88 (2H, d, $J = 8.7$ Hz), 3.79 (3H, s), 3.48–3.46 (2H, m), 2.95–2.88 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 130.2, 127.5, 119.5, 114.4, 55.3, 50.9, 34.5, 34.1 ppm; IR (KBr) ν 2251 (CN), 2107 (N_3) cm^{-1}; MS (EI) m/z (%) 216 (4) $[M]^+$, 188 (100), 145 (30), 121 (93). Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.07; H, 5.60; N, 25.79.

4.1.5.2. β-Azido-α-(*p*-methylphenylmethyl)propionitrile 10c. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (2H, d, $J = 8.3$ Hz), 7.16 (2H, d, $J = 8.3$ Hz), 3.57–3.48 (2H, m), 3.03–2.93 (3H, m), 2.37 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 132.4, 130.0, 129.0, 119.5, 50.9, 35.0, 34.0, 21.1 ppm; IR (KBr) ν 2244 (CN), 2107 (N_3) cm^{-1}; MS (EI) m/z (%) 172 (100) $[M-28]^+$, 171 (34), 157 (50), 144 (24), 143 (25), 119 (27), 118 (22), 105 (77). Anal. Calcd for $C_{11}H_{12}N_4$: C, 65.98; H, 6.04; N, 27.98. Found: C, 65.82; H, 5.97; N, 27.98.

4.1.5.3. β-Azido-α-(*p*-fluorophenylmethyl)propionitrile 10d. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.13 (2H, m), 7.00–6.94 (2H, m), 3.42 (2H, d, $J = 8.3$ Hz), 2.91–2.83 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.3 (d, $J = 243.7$ Hz), 131.2 (d, $J = 3.2$ Hz), 130.7 (d, $J = 8.1$ Hz), 119.1, 115.9 (d, $J = 21.4$ Hz), 50.9, 34.5, 34.0 ppm; IR (KBr) ν 2248 (CN), 2109 (N_3), 1509 cm^{-1}; MS (EI) m/z (%) 176 (100) $[M-28]^+$, 175 (48), 161 (15), 158 (27), 149 (24), 148 (52), 109 (32). Anal. Calcd for $C_{10}H_9N_4F$: C, 58.82; H, 4.44; N, 27.44. Found: C, 58.72; H, 4.52; N, 27.27.

4.1.5.4. β-Azido-α-(*p*-chlorophenylmethyl)propionitrile 10e. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (2H, d, $J = 8.4$ Hz), 7.21 (2H, d, $J = 8.4$ Hz), 3.53 (2H, d, $J = 3.7$ Hz), 3.00–2.93 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.9, 133.7, 130.5, 129.2, 119.0, 50.9, 34.7, 33.8 ppm; IR (KBr) ν 2248 (CN), 2108 (N_3) cm^{-1}; MS (EI) m/z (%) 194 (8) $[M-26]^+$, 192 (25), 165 (15), 163 (34), 141 (12), 139 (31), 127 (31), 125 (100). Anal. Calcd for $C_{10}H_9N_4Cl$: C, 54.43; H, 4.11; N, 25.39. Found: C, 54.50; H, 4.09; N, 25.29.

4.1.5.5. β-Azido-α-(*m*-chlorophenylmethyl)propionitrile 10f. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33–7.16 (4H, m), 3.55 (2H, d, $J = 5.7$ Hz), 3.04–2.95 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 134.8, 130.5, 129.2, 128.0, 127.3, 119.0, 50.9, 35.0, 33.7 ppm; IR (KBr) ν 2248 (CN), 2109 (N_3), 1289 cm^{-1}; MS (EI) m/z (%) 194 (15) $[M-26]^+$, 193 (17), 192 (52), 191 (41), 163 (28), 157 (73), 141 (19), 139 (68), 128 (55), 127 (31), 125 (100). Anal. Calcd for $C_{10}H_9N_4Cl$: C, 54.43; H, 4.11; N, 25.39. Found: C, 54.54; H, 4.11; N, 25.35.

4.1.5.6. β-Azido-α-(*o*-chlorophenylmethyl)propionitrile 10g. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.28 (4H, m), 3.61 (1H, dd, $J = 7.5$, 12.4 Hz), 3.56 (1H, dd, $J = 5.4$, 12.4 Hz), 3.22–3.07 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.0, 133.5, 131.7, 130.0, 129.3, 127.4, 119.1, 51.3, 33.7, 32.2 ppm; IR (KBr) ν 2245 (CN), 2108 (N_3) cm^{-1}; MS (EI) m/z (%) 194 (22) $[M-26]^+$, 192 (81), 157 (100), 127 (25), 125 (84). Anal. Calcd for $C_{10}H_9N_4Cl$: C, 54.43; H, 4.11; N, 25.39. Found: C, 54.36; H, 4.13; N, 25.61.

4.1.5.7. β-Azido-α-(*p*-bromophenylmethyl)propionitrile 10h. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (2H, d, $J = 8.4$ Hz), 7.05 (2H, d, $J = 8.4$ Hz), 3.40 (2H, d, $J = 8.2$ Hz), 2.92–2.83 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5, 132.1, 130.8, 121.7, 119.1, 50.9, 34.7, 33.7 ppm; IR (KBr) ν 2245 (CN), 2109 (N_3) cm^{-1}; MS (EI) m/z (%) 238 (97) $[M-28]^+$, 236 (100), 169 (65), 171 (64), 157 (84), 140 (33). Anal. Calcd for $C_{10}H_9N_4Br$: C, 45.30; H, 3.42; N, 21.13. Found: C, 45.11; H, 3.38; N, 21.03.

4.1.5.8. β-Azido-α-cyclohexylmethylpropionitrile 10i. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.52 (2H, d, $J = 6.3$ Hz), 2.90–2.80 (1H, m), 1.76–0.91 (13H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.0, 52.4, 37.0, 35.2, 33.5, 32.2, 29.9, 26.2, 25.9, 25.8 ppm; IR (KBr) ν 2233 (CN), 2105 (N_3) cm^{-1}; MS (EI) m/z (%) 164 (12) $[M-28]^+$, 135(3), 121 (100), 108 (16). Anal. Calcd for $C_{10}H_{16}N_4$: C, 62.47; H, 8.39; N, 29.14. Found: C, 62.25; H, 8.12; N, 29.37.

4.1.5.9. β-Azido-α-cyclopropylmethylpropionitrile 10j. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.61 (1H, dd, $J = 12.3$, 6.8 Hz), 3.56 (1H, dd, $J = 12.3$, 6.1 Hz), 2.90–2.81 (1H, m), 1.70–1.63 (1H, m), 1.57–1.50 (1H, m), 0.93–0.79 (1H, m), 0.68–0.53 (2H, m), 0.28–0.11 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.9, 51.7, 34.5, 32.7, 8.3, 4.9, 4.4 ppm; IR (KBr) ν 2244 (CN), 2108 (N_3) cm^{-1}; MS (EI) m/z (%) 122 (38) $[M-28]^+$, 107(9), 93 (34), 82 (75), 81 (100). Anal. Calcd for $C_7H_{10}N_4$: C, 55.98; H, 6.71; N, 37.31. Found: C, 56.16; H, 6.52; N, 37.04.

4.1.5.10. α-Azidomethylpentanenitrile 10k. Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.55 (1H, dd, $J = 12.3$, 6.8 Hz), 3.50 (1H, dd, $J = 12.3$, 6.1 Hz), 2.81–2.72 (1H, m), 1.73–1.43 (4H, m), 0.98 (3H, t, $J = 7.1$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 119.8, 52.0, 32.1, 31.5, 20.1,

13.5 ppm; IR (KBr) ν 2240 (CN), 2107 (N_3) cm^{-1}; MS (EI) m/z (%) 110 (15) $[M-28]^+$, 95(34), 81 (46), 54 (100). Anal. Calcd for $C_6H_{10}N_4$: C, 52.16; H, 7.29; N, 40.55. Found: C, 51.98; H, 7.33; N, 40.69.

4.2. General procedure for the biotransformations of nitriles

To an Erlenmeyer flask (150 ml) with a screw cap was added *R. erythropolis* AJ270 cells[15] (2 g wet weight) and potassium phosphate buffer (0.1 M, pH 7.0, 50 ml); the resting cells were activated at 30 °C for 0.5 h with orbital shaking. The racemic nitrile was added in one portion to the flask and the mixture incubated at 30 °C using an orbital shaker (200 rpm). The reaction, monitored by TLC and HPLC, was quenched after a specified period of time (see Tables 1 and 2) 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 (3×60 ml) gave, after drying over $MgSO_4$, concentration and a silica gel column chromatography eluting with a mixture of petroleum ether and acetone (2:1), the amide product. The aqueous solution was then acidified using aqueous HCl (2 M) to pH 2 and extracted with ethyl acetate (3×60 ml). The acid product was obtained after drying over $MgSO_4$, removal of the solvent under vacuum, followed by a silica gel column chromatography eluted with a mixture of petroleum ether and acetone (from 20:1 to 2:1). All products were characterized by their spectral data and comparison of the melting points and specific rotation with that of the known compounds, which are listed as follows, or by full characterization. The absolute configurations of α-arylmethyl-β-azidopropanoic acids **12b–h** and amides **11b–h** are tentatively assigned as (*R*) and (*S*), respectively, as that of **12a** and **11a**, based on the assumption that the introduction of a substituent on the benzene ring does not cause an inversion of the sign of the specific rotation. For other chiral products, absolute configurations were not determined. Enantiomeric excess values were obtained from HPLC analysis (see SI).

4.2.1. (−)-α-Azidophenylacetoamide 2. Mp 112–114 °C; $[\alpha]_D^{25} = -112.2$ (*c* 2.300, $CHCl_3$); ee 64.5% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (5H, s), 6.44 (1H, br), 6.39 (1H, br), 5.02 (1H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9, 134.7, 129.3, 129.2, 127.8, 67.1 ppm; IR (KBr) ν 3426, 3162 ($CONH_2$), 2106 (N_3), 1662 cm^{-1} (C=O); MS (EI) m/z (%) 148 (2) $[M-28]^+$, 132 (9), 120 (5), 104 (100). Anal. Calcd for $C_8H_8N_4O$: C, 54.54; H, 4.58; N, 31.80. Found: C, 54.47; H, 4.61; N, 31.78.

4.2.2. (−)-α-Azido-β-phenylpropanamide 5. Mp 79–80 °C; $[\alpha]_D^{25} = -35.8$ (*c* 2.850, $CHCl_3$); ee 36.6% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.26 (5H, m), 6.24 (1H, br), 6.08 (1H, br), 4.19 (1H, dd, $J = 8.4$, 4.3 Hz), 3.35 (1H, dd, $J = 14.1$, 4.3 Hz), 3.02 (1H, dd, $J = 14.1$, 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 136.1, 129.5, 128.7, 127.3, 65.3, 38.6 ppm; IR (KBr) ν 3451, 3184 ($CONH_2$), 2131, 2102 (N_3), 1672 cm^{-1} (C=O); MS (EI) m/z (%) 162 (30) $[M-28]^+$, 147 (19), 131 (4), 118 (30), 91 (100). Anal. Calcd for $C_9H_{10}N_4O$: C, 56.83; H, 5.30; N, 29.46. Found: C, 56.98; H, 5.36; N, 29.72.

4.2.3. (−)-α-Azido-β-phenylpropanoic acid 6. Oil; $[\alpha]_D^{25} = -25.2$ (*c* 2.300, $CHCl_3$); ee 45.0% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 10.90 (1H, br) 7.37–7.24 (5H, m), 4.16 (1H, dd, $J = 9.0$, 5.0 Hz), 3.24 (1H, dd, $J = 14.1$, 5.0 Hz), 3.04 (1H, dd, $J = 14.1$, 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.2, 135.6, 129.2, 128.8, 127.5, 63.1, 37.5 ppm; IR (KBr) ν 3445–2600 (COOH), 2116 (N_3), 1719 cm^{-1} (C=O); MS (EI) m/z (%) 191 (2) $[M]^+$, 163 (3) 148 (1), 119 (50), 118 (33), 92 (41), 91 (100). Anal. Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.54; H, 4.87; N, 21.63.

4.2.4. (+)-4-Azido-2-phenylbutanamide 8. Mp 56–60 °C; $[\alpha]_D^{25} = +64.3$ (*c* 2.425, $CHCl_3$); ee 56.4% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.27 (5H, m), 5.74 (1H, br), 5.45 (1H, br), 3.58 (1H, t, $J = 7.6$ Hz), 3.37–3.29 (1H, m), 3.25–3.16 (1H, m), 2.48–2.37 (1H, m), 2.05–1.93 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 138.7, 129.2, 128.0, 127.8, 49.4, 49.2, 32.1 ppm; IR (KBr) ν 3406, 3184 ($CONH_2$), 2102, 2083 (N_3), 1654 cm^{-1} (C=O); MS (EI) m/z (%) 176 (1) $[M-28]^+$, 173 (7), 159 (100), 130 (85). Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.93; H, 5.89; N, 27.44.

4.2.5. (+)-4-Azido-2-phenylbutanoic acid 9. Mp 66–68 °C; $[\alpha]_D^{25} = +64.0$ (*c* 1.000, $CHCl_3$); ee 83.0% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.37–7.25 (5H, m), 3.73 (1H, t, $J = 7.6$ Hz), 3.36–3.28 (1H, m), 3.23–3.14 (1H, m), 2.40–2.28 (1H, m), 2.09–1.97 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 137.1, 129.0, 128.1, 127.9, 49.0, 48.3, 31.9 ppm; IR (KBr) ν 3065–2517 (COOH), 2141, 2089 (N_3), 1695 cm^{-1} (C=O); MS (EI) m/z (%) 177 (2) $[M-28]^+$, 161 (60), 159 (71), 132 (58), 130 (100), 118 (48), 117 (95). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.45; H, 5.39; N, 20.53.

4.2.6. (*S*)-β-Azido-α-benzylpropanamide 11a. Oil; $[\alpha]_D^{25} = -31.9$ (*c* 2.950, $CHCl_3$); ee >99% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 7.38–7.18 (5H, m), 5.77 (1H, br), 5.52 (1H, br), 3.61 (1H, dd, $J = 12.1$, 8.5 Hz), 3.42 (1H, dd, $J = 12.1$, 4.9 Hz), 2.94 (1H, dd, $J = 13.6$, 8.5 Hz), 2.80 (1H, dd, $J = 13.6$, 6.6 Hz), 2.65–2.61 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 138.1, 128.9, 128.8, 126.9, 52.3, 48.5, 36.2 ppm; IR (KBr) ν 3334, 3188 ($CONH_2$), 2103 (N_3), 1668 cm^{-1} (C=O); MS (EI) m/z (%) 176 (25) $[M-28]^+$, 159 (66), 158 (30), 146 (17), 132 (34), 131 (50), 130 (100). Anal. Calcd for $C_{10}H_{12}N_4O$: C, 58.81; H, 5.92; N, 27.43. Found: C, 58.44; H, 5.82; N, 27.83.

4.2.7. (*R*)-β-Azido-α-benzylpropanoic acid 12a. Oil; $[\alpha]_D^{25} = -29.0$ (*c* 2.000, $CHCl_3$); ee >99% (chiral HPLC analysis); ^1H NMR (300 MHz, $CDCl_3$) δ 11.36 (1H, br) 7.35–7.18 (5H, m), 3.49 (2H, d, $J = 5.8$ Hz), 3.12–3.05 (1H, m), 2.95–2.16 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 137.4, 129.0, 128.8, 127.0, 50.9, 46.7, 34.9 ppm; IR (KBr) ν 3086–2608 (COOH), 2104 (N_3), 1710 cm^{-1} (C=O); MS (EI) m/z (%) 177 (11) $[M-28]^+$, 176 (9), 147

(19), 133 (48), 132 (100), 130 (36), 117 (32), 115 (28), 91 (36). Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.25; H, 5.39; N, 20.71.

4.2.8. (*S*)-β-Azido-α-(*p*-methoxyphenylmethyl)propanamide 11b. Mp 73–74 °C; $[\alpha]_D^{25} = -29.9$ (*c* 1.625, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (2H, d, $J = 8.7$ Hz), 6.85 (2H, d, $J = 8.7$ Hz), 6.00 (1H, br), 5.72 (1H, br), 3.79 (3H, s), 3.59 (1H, dd, $J = 12.2$, 8.5 Hz), 3.40 (1H, dd, $J = 12.2$, 4.9 Hz), 2.89 (1H, dd, $J = 13.7$, 8.4 Hz), 2.75 (1H, dd, $J = 13.7$, 6.6 Hz), 2.63–2.60 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 158.4, 130.1, 129.9, 114.1, 55.2, 52.3, 48.5, 35.3 ppm; IR (KBr) *v* 3337, 3194 ($CONH_2$), 2103 (N_3), 1668 (C=O) cm^{-1}; MS (ESI$^+$) *m*/*z* 256.7 $[M+Na]^+$. Anal. Calcd for $C_{11}H_{14}N_4O_2$: C, 56.40; H, 6.02; N, 23.92. Found: C, 56.38; H, 6.01; N, 24.09.

4.2.9. (*R*)-β-Azido-α-(*p*-methoxyphenylmethyl)propanoic acid 12b. Oil; $[\alpha]_D^{25} = -38.2$ (*c* 2.010, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (1H, br) 7.14 (2H, d, $J = 8.7$ Hz), 6.89 (2H, d, $J = 8.7$ Hz), 3.83 (3H, s), 3.52–3.50 (2H, m), 3.09–3.04 (1H, m), 2.94–2.81 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 158.5, 130.0, 129.4, 114.2, 55.3, 51.0, 46.9, 34.1 ppm; IR (KBr) *v* 3038–2555 (COOH), 2104 (N_3), 1710 (C=O) cm^{-1}; MS (ESI$^+$) *m*/*z* 257.9 $[M+Na]^+$. Anal. Calcd for $C_{11}H_{13}N_3O_3$: C, 56.16; H, 5.57; N, 17.86. Found: C, 56.04; H, 5.47; N, 17.86.

4.2.10. (*S*)-β-Azido-α-(*p*-methylphenylmethyl)propanamide 11c. Mp 79–80 °C; $[\alpha]_D^{25} = -34.9$ (*c* 2.980, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (2H, d, $J = 8.2$ Hz), 7.00 (2H, d, $J = 8.2$ Hz), 5.55 (1H, br), 5.43 (1H, br), 3.53 (1H, dd, $J = 12.1$, 8.4 Hz), 3.35 (1H, dd, $J = 12.1$, 4.8 Hz), 2.83 (1H, dd, $J = 13.6$, 8.4 Hz), 2.69 (1H, dd, $J = 13.6$, 6.5 Hz), 2.56–2.52 (1H, m), 2.25 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9, 136.5, 135.0, 129.4, 128.7, 52.3, 48.5, 35.8, 21.0 ppm; IR (KBr) *v* 3390, 3199 ($CONH_2$), 2100 (N_3), 1642 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 218 (1) $[M]^+$, 190 (51), 173 (84), 160 (36), 146 (64), 145 (84), 144 (100), 130 (51), 105 (49). Anal. Calcd for $C_{11}H_{14}N_4O$: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.45; H, 6.53; N, 25.57.

4.2.11. (*R*)-β-Azido-α-(*p*-methylphenylmethyl)propanoic acid 12c. Oil; $[\alpha]_D^{25} = -34.0$ (*c* 2.705, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.44 (1H, br) 7.16 (2H, d, $J = 8.1$ Hz), 7.11 (2H, d, $J = 8.1$ Hz), 3.51 (2H, d, $J = 5.0$ Hz), 3.12–3.06 (1H, m), 2.96–2.82 (2H, m), 2.36 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 136.5, 134.3, 129.4, 128.8, 51.0, 46.8, 34.6, 21.0 ppm; IR (KBr) *v* 3024–2562 (COOH), 2103 (N_3), 1709 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 191 (29) $[M-28]^+$, 176 (27), 147 (78), 146 (100), 132 (84), 105 (44). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.17. Found: C, 60.38; H, 6.03; N, 19.39.

4.2.12. (*S*)-β-Azido-α-(*p*-fluorophenylmethyl)propanamide 11d. Mp 80–81 °C; $[\alpha]_D^{25} = -34.5$ (*c* 2.495, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.19–7.15 (2H, m), 7.04–6.98 (2H, m), 5.88 (1H, br), 5.65 (1H, br), 3.61 (1H, dd, $J = 12.2$, 8.4 Hz), 3.44 (1H, dd, $J = 12.2$, 5.0 Hz), 2.93 (1H, dd, $J = 13.7$, 8.6 Hz), 2.79 (1H, dd, $J = 13.7$, 6.4 Hz), 2.63–2.60 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8, 161.8 (d, $J = 243.7$ Hz), 133.7 (d, $J = 3.2$ Hz), 130.3 (d, $J = 7.9$ Hz), 115.6 (d, $J = 21.2$ Hz), 52.3, 48.6, 35.3 ppm; IR (KBr) *v* 3338, 3194 ($CONH_2$), 2104 (N_3), 1668 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 194 (8) $[M-28]^+$, 178 (64), 161 (42), 148 (54), 133 (50), 109 (100). Anal. Calcd for $C_{10}H_{11}N_4OF$: C, 54.04; H, 4.99; N, 25.21. Found: C, 54.01; H, 4.93; N, 25.33.

4.2.13. (*R*)-β-Azido-α-(*p*-fluorophenylmethyl)propanoic acid 12d. Oil; $[\alpha]_D^{25} = -27.3$ (*c* 2.125, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.75 (1H, br) 7.20–7.16 (2H, m), 7.06–7.00 (2H, m), 3.52 (2H, d, $J = 5.6$ Hz), 3.09–3.03 (1H, m), 2.93–2.87 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.1, 161.9 (d, $J = 243.7$ Hz), 133.1 (d, J =3.4 Hz), 130.4 (d, $J = 8.0$ Hz), 115.6 (d, $J = 21.2$ Hz), 50.9, 46.8, 34.0 ppm; IR (KBr) *v* 3121–2618 (COOH), 2105 (N_3), 1713 (C=O), 1511, 1223 cm^{-1}; MS (EI) *m*/*z* (%) 195 (17) $[M-28]^+$, 180 (16), 166 (14), 151 (77), 150 (100), 133 (34), 109 (77). Anal. Calcd for $C_{10}H_{10}N_3O_2F$: C, 53.81; H, 4.52; N, 18.83 Found: C, 53.56; H, 4.54; N, 19.14.

4.2.14. (*S*)-β-Azido-α-(*p*-chlorophenylmethyl)propanamide 11e. Mp 63–65 °C; $[\alpha]_D^{25} = -29.2$ (*c* 1.370, $CHCl_3$); ee 86.7% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 7.29 (2H, d, $J = 8.4$ Hz), 7.14 (2H, d, $J = 8.4$ Hz), 5.78 (1H, br), 5.58 (1H, br), 3.61 (1H, dd, $J = 12.2$, 8.4 Hz), 3.43 (1H, dd, $J = 12.2$, 5.1 Hz), 2.93 (1H, dd, $J = 13.7$, 8.7 Hz), 2.78 (1H, dd, $J = 13.7$, 6.3 Hz), 2.62–2.52 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 136.6, 132.7, 130.3, 128.9, 52.3, 48.4, 35.4 ppm; IR (KBr) *v* 3328, 3190 ($CONH_2$), 2102 (N_3), 1664 cm^{-1} (C=O); MS (EI) *m*/*z* (%) 238 (1) $[M]^+$, 212 (18), 210 (54), 196 (20), 194 (71), 167 (48), 166 (91), 165 (100), 164 (100), 158 (60), 132 (16), 130 (65), 127 (31), 125 (88). Anal. Calcd for $C_{10}H_{11}N_4OCl$: C, 50.32; H, 4.65; N, 23.47. Found: C, 50.55; H, 4.68; N, 23.27.

4.2.15. (*R*)-β-Azido-α-(*p*-chlorophenylmethyl)propanoic acid 12e. Oil; $[\alpha]_D^{25} = -24.6$ (*c* 1.055, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 10.40 (1H, br), 7.31 (2H, d, $J = 8.4$ Hz), 7.15 (2H, d, $J = 8.4$ Hz), 3.52 (2H, d, $J = 5.6$ Hz), 3.12–3.03 (1H, m), 2.94–2.85 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.0, 135.9, 132.9, 130.3, 128.9, 50.9, 46.6, 34.1 ppm; IR (KBr) *v* 3092–2566 (COOH), 2105 (N_3), 1711 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 239 (1) $[M]^+$, 213 (3), 211 (6), 169 (21), 168 (26), 167 (72), 166 (88), 132 (100), 127 (16), 125 (53). Anal. Calcd for $C_{10}H_{10}N_3O_2Cl$: C, 50.12; H, 4.21; N, 17.53. Found: C, 50.04; H, 4.16; N, 17.77.

4.2.16. (*S*)-β-Azido-α-(*m*-chlorophenylmethyl)propanamide 11f. Oil; $[\alpha]_D^{25} = -33.6$ (*c* 1.250, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 7.27–7.20 (3H, m), 7.11–7.06 (1H, m), 5.72 (1H, br), 5.57 (1H, br), 3.60 (1H, dd, $J = 12.1$, 8.5 Hz), 3.42 (1H, dd, $J = 12.1$, 5.1 Hz), 2.93 (1H, dd, $J = 13.6$, 8.6 Hz), 2.77 (1H, dd,

$J = 13.6$, 6.3 Hz), 2.66–2.56 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 140.2, 134.5, 130.0, 129.0, 127.15, 127.1, 52.4, 48.3, 35.7 ppm; IR (KBr) ν 3324, 2930 ($CONH_2$), 2102 (N_3), 1668 cm^{-1} (C=O); MS (ESI^+) m/z 262.3 $[M+2+Na]^+$, 260.9 $[M+Na]^+$. Anal. Calcd for $C_{10}H_{11}N_4OCl$: C, 50.32; H, 4.65; N, 23.47. Found: C, 50.34; H, 4.59; N, 23.32.

4.2.17. (*R*)-β-Azido-α-(*m*-chlorophenylmethyl)propanoic acid 12f. Oil; $[\alpha]_D^{25} = -31.8$ (c 1.130, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 9.23 (1H, br), 7.27–7.07 (4H, m), 3.50 (2H, d, $J = 5.5$ Hz), 3.08–3.04 (1H, m), 2.93–2.81 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.5, 139.5, 134.5, 130.0, 129.1, 127.2, 127.15, 50.9, 46.4, 34.4 ppm; IR (KBr) ν 3060–2569 (COOH), 2105 (N_3), 1711 (C=O) cm^{-1}; MS (EI) m/z (%) 240 (2) $[M]^+$, 213 (6), 211 (15), 169 (24), 168 (28), 167 (93), 166 (100), 132 (80), 127 (24), 125 (84). Anal. Calcd for $C_{10}H_{10}N_3O_2Cl$: C, 50.12; H, 4.21; N, 17.53. Found: C, 49.76; H, 4.11; N, 17.13.

4.2.18. (*S*)-β-Azido-α-(*o*-chlorophenylmethyl)propanamide 11g. Mp 85–87 °C; $[\alpha]_D^{25} = -39.6$ (c 2.575, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 7.39–7.33 (1H, m), 7.25–7.19 (3H, m), 6.12 (1H, br), 5.81 (1H, br), 3.64 (1H, dd, $J = 12.0$, 8.8 Hz), 3.41 (1H, dd, $J = 12.0$, 4.6 Hz), 2.03–2.93 (2H, m), 2.86–2.80 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0, 135.8, 133.9, 131.6, 129.8, 128.5, 127.1, 52.3, 46.0, 34.1 ppm; IR (KBr) ν 3390, 3197 ($CONH_2$), 2103 (N_3), 1665 cm^{-1} (C=O); MS (EI) m/z (%) 212 (5) $[M-26]^+$, 210 (16), 203 (46), 177 (13), 175 (100). Anal. Calcd for $C_{10}H_{11}N_4OCl$: C, 50.32; H, 4.65; N, 23.47. Found: C, 50.42; H, 4.66; N, 23.44.

4.2.19. (*R*)-β-Azido-α-(*o*-chlorophenylmethyl)propanoic acid 12g. Oil; $[\alpha]_D^{25} = -29.4$ (c 2.855, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 10.83 (1H, br), 7.43–7.38 (1H, m), 7.30–7.22 (3H, m), 3.59–3.54 (2H, m), 3.26–3.20 (1H, m), 3.11–3.00 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.2, 135.4, 134.2, 131.5, 129.9, 128.6, 127.1, 51.3, 44.8, 32.8 ppm; IR (KBr) ν 3059–2558 (COOH), 2104 (N_3), 1712 (C=O) cm^{-1}; MS (EI) m/z (%) 213 (2) $[M-26]^+$, 211 (6), 178 (22), 169 (5), 168 (10), 167 (20), 166 (29), 147 (22), 132 (100). Anal. Calcd for $C_{10}H_{10}N_3O_2Cl$: C, 50.12; H, 4.21; N, 17.53. Found: C, 50.03; H, 4.15; N, 17.76.

4.2.20. (*S*)-β-Azido-α-(*p*-bromophenylmethyl)propanamide 11h. Mp 75–76 °C; $[\alpha]_D^{25} = -29.1$ (c 1.445, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 7.44 (2H, d, $J = 8.4$ Hz), 7.08 (2H, d, $J = 8.4$ Hz), 5.41 (2H, br), 3.61 (1H, dd, $J = 12.2$, 8.4 Hz), 3.43 (1H, dd, $J = 12.2$, 5.1 Hz), 2.91 (1H, dd, $J = 13.6$, 8.8 Hz), 2.76 (1H, dd, $J = 13.6$, 6.2 Hz), 2.52–2.62 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 137.1, 131.8, 130.6, 120.8, 52.4, 48.3, 35.5 ppm; IR (KBr) ν 3386, 3196 ($CONH_2$), 2116 (N_3), 1645 cm^{-1} (C=O); MS (EI) m/z (%) 256 (36) $[M-26]^+$, 254 (37), 239 (39), 238 (54), 237 (40), 236 (37), 226 (43), 211 (84), 210 (100), 209 (71), 208 (58), 171 (59), 158 (62), 130 (60). Anal. Calcd for $C_{10}H_{11}N_4OBr$: C, 42.42; H, 3.92; N, 19.79. Found: C, 42.13; H, 3.88; N, 19.73.

4.2.21. (*R*)-β-Azido-α-(*p*-bromophenylmethyl)propanoic acid 12h. Oil; $[\alpha]_D^{25} = -29.5$ (c 1.220, $CHCl_3$); ee 93.6% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 7.44 (2H, d, $J = 8.4$ Hz), 7.08 (2H, d, $J = 8.4$ Hz), 3.50 (2H, d, $J = 5.7$ Hz), 3.04–2.99 (1H, m), 2.92–2.81 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7, 136.4, 131.9, 130.7, 120.9, 50.9, 46.5, 34.2 ppm; IR (KBr) ν 3089–2564 (COOH), 2105 (N_3), 1711 (C=O) cm^{-1}; MS (EI) m/z (%) 285 (3) $[M+2]^+$, 283 (3), 257 (4), 255 (4), 213 (59), 212 (61), 211 (73), 210 (74), 171 (47), 169 (47), 132 (100), 115 (37). Anal. Calcd for $C_{10}H_{10}N_3O_2Br$: C, 42.27; H, 3.55; N, 14.79. Found: C, 42.31; H, 3.62; N, 14.58.

4.2.22. (−)-β-Azido-α-cyclohexylmethylpropanamide 11i. Mp 82–83 °C; $[\alpha]_D^{25} = -28.2$ (c 2.800, $CHCl_3$); ee >99% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 5.83 (1H, br), 5.70 (1H, br), 3.55 (1H, dd, $J = 12.1$, 8.9 Hz), 3.37 (1H, dd, $J = 12.1$, 4.8 Hz), 2.51–2.48 (1H, m), 1.72–1.54 (6H, m), 1.31–1.18 (5H, m), 0.93–0.81 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 53.4, 43.8, 37.6, 35.2, 33.6, 33.1, 26.4, 26.1 ppm; IR (KBr) ν 3403, 3220 ($CONH_2$), 2091 (N_3), 1640 cm^{-1} (C=O); MS (EI) m/z (%) 182 (2) $[M-28]^+$, 164 (15), 139 (9), 135 (5), 121 (100), 108 (17). Anal. Calcd for $C_{10}H_{18}N_4O$: C, 57.12; H, 8.63; N, 26.64. Found: C, 57.23; H, 8.59; N, 26.41.

4.2.23. (+)-β-Azido-α-cyclohexylmethylpropanoic acid 12i. Oil; $[\alpha]_D^{25} = +6.0$ (c 4.300, $CHCl_3$); ee 95.6% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 3.54 (1H, dd, $J = 12.2$, 8.2 Hz), 3.44 (1H, dd, $J = 12.2$, 5.2 Hz), 2.76–2.72 (1H, m), 1.81–1.55 (6H, m), 1.44–1.08 (5H, m), 0.99–0.83 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.2, 52.6, 42.7, 37.1, 35.2, 33.3, 32.9, 26.4, 26.0 ppm; IR (KBr) ν 3037–2555 (COOH), 2102 (N_3), 1710 (C=O), 1450, 1274 cm^{-1}; MS (EI) m/z (%) 183 (9) $[M-28]^+$, 154 (3), 140 (100). Anal. Calcd for $C_{10}H_{17}N_3O_2$: C, 56.85; H, 8.11; N, 19.89. Found: C, 56.90; H, 8.03; N, 20.10.

4.2.24. (−)-β-Azido-α-cyclopropylmethylpropanamide 11j. Mp 64–66 °C; $[\alpha]_D^{25} = -29.8$ (c 1.945, $CHCl_3$); ee 83.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 6.06 (1H, br), 5.81 (1H, br), 3.63 (1H, dd, $J = 12.1$, 8.8 Hz), 3.45 (1H, dd, $J = 12.1$, 5.0 Hz), 2.55–2.46 (1H, m), 1.67–1.58 (1H, m), 1.39–1.30 (1H, m), 0.75–0.70 (1H, m), 0.53–0.46 (2H, m), 0.14–0.05 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8, 52.7, 47.0, 35.1, 8.8, 4.8, 4.5 ppm; IR (KBr) ν 3386, 3196 ($CONH_2$), 2110 (N_3), 1654 cm^{-1} (C=O); MS (EI) m/z (%) 140 (17) $[M-28]^+$, 126 (100). Anal. Calcd for $C_7H_{12}N_4O$: C, 49.99; H, 7.19; N, 33.31. Found: C, 49.78; H, 7.19; N, 32.98.

4.2.25. β-Azido-α-cyclopropylmethylpropanoic acid 12j. Oil; $[\alpha]_D^{25} = 0$ (c 2.800, $CHCl_3$); ee 58.6% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 11.90 (1H, br), 3.65 (1H, dd, $J = 12.2$, 8.0 Hz), 3.56 (1H, dd, $J = 12.2$, 5.4 Hz), 2.80–2.71 (1H, m), 1.68–1.49 (2H, m), 0.81–0.68 (1H, m), 0.57–0.46 (2H, m), 0.13–0.08 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.4, 51.7, 45.8, 34.3, 8.4, 4.7, 4.5 ppm; IR (KBr) ν 3081–2566 (COOH), 2104 (N_3), 1711 (C=O) cm^{-1}; MS (EI) m/z (%) 141 (3) $[M-28]^+$, 140 (5), 127 (46), 97 (31), 82 (38), 68 (100). Anal. Calcd

for $C_7H_{11}N_3O_2$: C, 49.70; H, 6.55; N, 24.84. Found: C, 49.75; H, 6.43; N, 24.83.

4.2.26. (−)-α-Azidomethylpentanamide 11k. Mp 63–65 °C; $[\alpha]_D^{25} = -12.2$ (*c* 1.880, $CHCl_3$); ee 65.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 6.07 (1H, br), 5.80 (1H, br), 3.58 (1H, dd, $J = 12.1$, 8.8 Hz), 3.39 (1H, dd, $J = 12.1$, 4.9 Hz), 2.45–2.34 (1H, m), 1.69–1.58 (1H, m), 1.45–1.34 (3H, m), 0.93 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.9, 53.0, 46.4, 32.2, 20.4, 14.0 ppm; IR (KBr) *v* 3407, 3332, 3294, 3209 ($CONH_2$), 2107 (N_3), 1656 cm^{-1} (C=O); MS (EI) *m*/*z* (%) 128 (25) $[M-28]^+$, 114(10), 99 (60), 82 (36), 72 (100). Anal. Calcd for $C_6H_{12}N_4O$: C, 46.14; H, 7.74; N, 35.87. Found: C, 46.13; H, 7.83; N, 35.72.

4.2.27. (−)-α-Azidomethylpentanoic acid 12k. Oil; $[\alpha]_D^{25} = -2.6$ (*c* 1.175, $CHCl_3$); ee 75.0% (chiral HPLC analysis); ^{1}H NMR (300 MHz, $CDCl_3$) 11.50 (1H, br), 3.57 (1H, dd, $J = 12.2$, 8.2 Hz), 3.46 (1H, dd, $J = 12.2$, 5.3 Hz), 2.68–2.59 (1H, m), 1.74–1.62 (1H, m), 1.59–1.49 (1H, m), 1.48–1.33 (2H, m), 0.95 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.8, 52.1, 45.0, 31.5, 20.1, 13.9 ppm; IR (KBr) *v* 3037–2551 (COOH), 2103 (N_3), 1710 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 129 (3) $[M-28]^+$, 114 (8), 100 (11), 87 (19), 73 (100), 55 (35). Anal. Calcd for $C_6H_{11}N_3O_2$: C, 45.85; H, 7.05; N, 26.74. Found: C, 45.86; H, 6.98; N, 26.46.

4.3. Preparation of (*S*)-β-azido-α-benzylpropanoic acid 12a

A mixture of (*S*)-**11a** (182 mg, ee >99.5%) in hydrochloric acid (6 M, 8 ml) was stirred at 55 °C for 43 h. Water (60 ml) was added and the mixture was extracted with dichloromethane (3 × 20 ml). After drying over $MgSO_4$ and removal of the solvent under vacuum, (*S*)-β-azido-α-benzylpropanoic acid (*S*)-**12a** (176 mg, 96%) was obtained as colorless liquid: $[\alpha]_D^{25} = +31.1$ (*c* 2.950, $CHCl_3$), ee >99.5% (chiral HPLC analysis).

4.4. Synthesis of (*S*)- and (*R*)-α-benzyl-β-amino acids

(*S*)-**12a** (151 mg, 0.74 mmol, ee >99.5%) was dissolved in methanol (15 ml) followed by the addition of 10% Pd/C catalyst (74 mg). The mixture was then stirred at room temperature under hydrogen atmosphere for 3 h. Water (15 ml) was then added and the mixture was stirred for another 30 min. Filtration and concentration gave (*S*)-(−)-α-benzyl-β-aminopropanoic acid (*S*)-(−)-**13** (122 mg, 93%) as a white powder: mp 209–212 °C (lit.[22] mp 224–225 °C); $[\alpha]_D^{25} = -17.3$ (*c* 1.850, 1 M HCl) {lit.[22] $[\alpha]_D^{25} = -11.0$ (*c* 1.000, 1 M HCl)]}; ^{1}H NMR (300 MHz, D_2O) 7.34–7.23 (5H, m), 3.08–2.95 (3H, m), 2.85–2.80 (2H, m); IR (KBr) *v* 3420 ($CONH_2$), 3027–2628 (COOH), 1633 (C=O) cm^{-1}. Hydrogenation of (*R*)-**12a** gave (*R*)-(+)-**13**: $[\alpha]_D^{25} = +16.9$ (*c* 2.250, 1 M HCl) [lit.[22] $[\alpha]_D^{25} = +11.3$ (*c* 1.000, 1 M HCl)].

4.5. Preparation of diethyl 1-[(2*S*-carbamoyl-3-phenyl)-propyl]-1*H*-[1,2,3]triazole-4,5-dicarboxylate 14

A mixture of (*S*)-**11a** (204 mg, 1 mmol) and diethyl acetylenedicarboxylate (187 mg, 1.1 mmol) was refluxed in ethanol (5 ml) for 12 h. After removal of the ethanol under vacuum followed by silica gel column chromatography eluting with a mixture of petroleum ether and acetone (1.5:1), diethyl 1-(2*S*-carbamoyl-3-phenyl)propyl-1*H*-[1,2,3]triazole-4,5-dicarboxylate **14** (337 mg, 90%) was obtained as an oil: $[\alpha]_D^{25} = -72.6$ (*c* 1.350, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 7.29–7.18 (5H, m), 5.95 (1H, br), 5.61 (1H, br), 4.92 (1H, dd, $J = 13.7$, 9.0 Hz), 4.55 (1H, dd, $J = 13.7$, 5.4 Hz), 4.43 (2H, q, $J = 7.1$ Hz), 4.38 (2H, q, $J = 7.1$ Hz), 3.46–3.36 (1H, m), 3.04 (1H, dd, $J = 13.7$, 8.7 Hz), 2.83 (1H, dd, $J = 13.7$, 6.4 Hz), 1.39 (3H, t, $J = 7.3$ Hz), 1.30 (3H, t, $J = 7.6$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 160.0, 158.5, 139.6, 137.6, 131.2, 128.9, 128.7, 126.9, 63.1, 61.8, 51.1, 48.5, 36.6, 14.1, 13.9 ppm; IR (KBr) *v* 3333, 3195 ($CONH_2$), 1732, 1677 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 374 (5) $[M]^+$, 301 (13), 161 (60), 160 (79), 143 (84), 117 (85), 116 (74), 115 (92), 91 (100). Anal. Calcd for $C_{18}H_{22}N_4O_5$: C, 57.75; H, 5.92; N, 14.96. Found: C, 57.91; H, 6.02; N, 15.19.

4.6. Preparation of 1-[(2*R*-hydroxycarbonyl-3-phenyl)-propyl]-4-phenyl-1*H*-1,2,3-triazole 15

To a mixture of (*R*)-**12a** (205 mg, 1 mmol), *tert*-butanol (2.5 ml), and water (2 ml) were added consecutively phenylacetylene (1.5 mmol), aqueous sodium ascorbate (100 μl, 1 M), and aqueous copper(II) sulfate (100 μl, 0.1 M). The resulting mixture was stirred at room temperature for 2 h. Water (25 ml) was added and the mixture extracted with ethyl acetate (3 × 15 ml). After drying over $MgSO_4$ and concentration, the residue was passed through a silica gel column eluted with a mixture of petroleum ether and acetone (1.5:1) to afford 1-[(2*R*-hydroxycarbonyl-3-phenyl)propyl]-4-phenyl-1*H*-1,2,3-triazole **15** (310 mg, 100%) as a white powder: mp 141–143 °C; $[\alpha]_D^{25} = +7.2$ (*c* 1.955, MeOH); ^{1}H NMR (300 MHz, DMSO-d_6) 12.6 (1H, br), 8.54 (1H, s), 7.84 (2H, d, $J = 8.0$ Hz), 7.45 (2H, t, $J = 7.6$ Hz), 7.35–7.20 (6H, m), 4.62 (1H, dd, $J = 13.8$, 8.4 Hz), 4.51 (1H, dd, $J = 13.7$, 5.6 Hz), 3.33 (1H, quin, $J = 6.8$ Hz), 2.98–2.84 (2H, m); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 146.1, 138.1, 130.7, 128.91, 128.86, 128.3, 127.8, 126.5, 125.1, 121.9, 50.5, 47.2, 35.0 ppm; IR (KBr) *v* 3137–2521 (COOH), 1715, 1702 (C=O) cm^{-1}; MS (EI) *m*/*z* (%) 307 (6) $[M]^+$, 278 (5), 145 (100). Anal. Calcd for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.13; H, 5.66; N, 13.77.

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