JOC The Journal of Organic Chemistry

A Tf2O-promoted Intramolecular Schmidt Reaction of the #-Azido Carboxylic Acids

Xue-Juan Wang, Yan Su, Rui Li, and Peiming Gu

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b00475 • Publication Date (Web): 18 Apr 2018

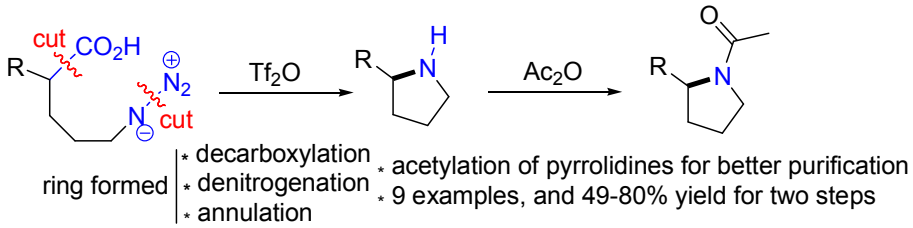
ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

A Tf_2O-promoted Intramolecular Schmidt Reaction of the ω-Azido Carboxylic Acids

Xue-Juan Wang, Yan Su, Rui Li, Peiming Gu*
Department of Chemistry, Ningxia University, Yinchuan 750021, China
Phone: +86(951)206-2274
Fax: +86(951)206-2323
E-mail: gupm@nxu.edu.cn

Tables of contents

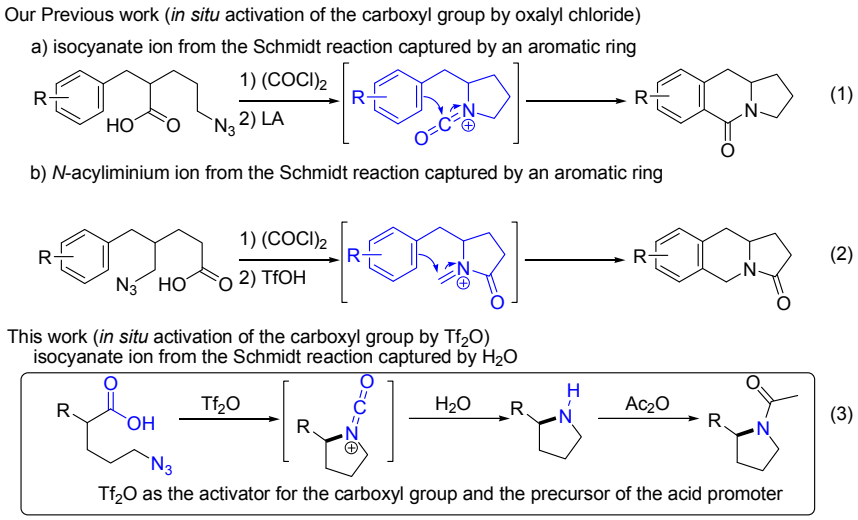


Abstract

A designed Tf_2O-promoted intramolecular Schmidt reaction of the 2-substituted ω-azido carboxylic acids was demonstrated. The Tf_2O was used as an activation reagent for the carboxylic acid, and the ω-azido anhydride was *in situ* generated with releasing a molecular TfOH, acting as an acid promoter for the Schmidt process. A series of 2-substituted pyrrolidines were produced and acetylated for better purification. The strategy was also efficient for conversion of a 4-substituted ω-azido carboxylic acid to the tricyclic lactam.

Main Text

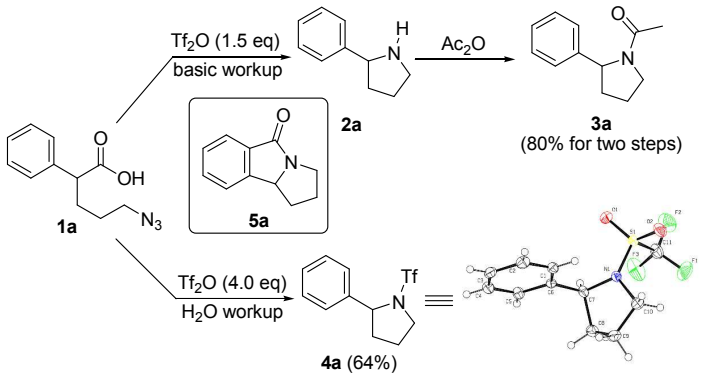
The Schmidt reaction is an acid-promoted reaction of an azide with an electrophile, and it involves the carbon-skeleton rearrangement and extrusion of nitrogen gas.[1] In the last thirty years, the alkyl azides were extensively explored for the Schmidt reaction, and they were demonstrated as the very successful substrates when the carbonyl compounds, ketones[3] and aldehydes[2], were used as the electrophiles. The conversion developed by Aubé's group provides a powerful strategy for construction of the nitrogen-containing molecules, especially for the synthesis of the bioactive nature products. However, the carboxylic acids were more challenging for the analogue reaction of alkyl azides, which might be due to their low reactivities. An *in situ* activation strategy of the carboxylic acids for the Schmidt reaction was reported in our group (Scheme 1), where the oxalyl chloride was employed as the activator for the carboxyl group, and then an additional acid promoter was added to facilitate the following rearrangement process.[4] In this paper, we report a designed Tf_2O-promoted intramolecular Schmidt reaction of several ω-azido carboxylic acids, and the addition of an acid promoter is reduced.



Scheme 1. The *in situ* activation strategy for Schmidt reaction of the ω-azido carboxylic acid

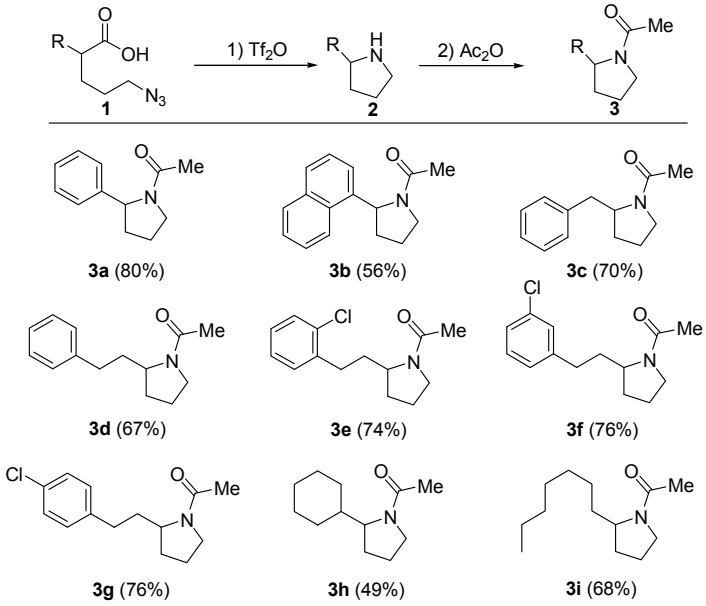
The key point of our previous *in situ* activation strategy relied on the replacement of the hydroxyl group of the carboxyl group with a chlorine atom, which might possess a better leaving aptitude during a nucleophilic addition. This manipulation would enhance a proposed aminodiazonium ion formation, resulting in the sequent skeleton rearrangement under the acidic conditions. Similarly, here we envisioned that the rearrangement reaction of the ω-azido carboxylic acid could proceed if the carboxylic acid was modified into a suitable mixed anhydride. It seems that generation of an organic mixed anhydride could be addressed from a carboxylic acid and another acid anhydride with releasing an additional acid,[5] and the newly generated acid was just required as an acid promoter for the Schmidt reaction. The TfOH has been identified as a good promoter for our reported Schmidt reaction of alkyl azides with acyl chlorides.[4b] Therefore, the Tf_2O might be a reasonable anhydride candidate for realizing this proposal. Certainly, further conversion of the isocyanate ion[4a,4c,4d] and/or *N*-acyliminium ion[4b,4c] from the rearrangement process to stable products should be necessary, otherwise they could not be easily isolated and identified.

To test the above hypothesis, the 2-phenyl ω-azido carboxylic acid **1a** was selected[4d] for the initial exploration (Scheme 2). To our delight, treatment of **1a** (0.5 mmol) in dichloromethane (2 mL) with 1.5 equiv of Tf_2O at room temperature for 12 h afforded an amine **2a** as its triflate. After the basic workup, the free amine **2a** could be isolated as the dominant product with 84-99% yield from several different trials, but all the samples were accompanied by some impurities. Therefore, further protection of **2a** with acetic anhydride was applied for better purification of the product. The amide **3a** was obtained with 80% yield for two steps, and the ^1H NMR and ^{13}C NMR of **3a** were congruent with those previously reported.[6] If more Tf_2O (4.0 equiv) was used, the triflamide **4a** would be delivered with 64% yield, whose structure was confirmed by X-ray analysis. The triflamide **4a** might be generated from the amine **2a** with the excessive Tf_2O, where the Tf_2O played three important roles of the activator for the substrate, a precursor of the acid promoter, and the protection reagent for the amine. Furthermore, the tricyclic lactam **5a**, a previously reported product[4d] from the Schmidt reaction activated by oxalyl chloride, was occasionally observed if the reaction was carried out in a heavier concentration.



Scheme 2. The Tf_2O-promoted Schmidt reaction of **1a**

Next, the scope of 2-substituted ω-azido carboxylic acid was explored, and the results were summarized in Scheme 3. The substrates examined here were prepared according to our previously reported procedure,[4] and they all could be delivered to the amides **3** with acceptable to good overall yields. Among them, the 2-naphenyl-1-acetylpyrrolidine **3b** and the 2-phenyl-1-acetylpyrrolidine **3c** were obtained in 56% and 70% yields. For these two cases, the tricyclic lactams **5b** and **5c** (not shown in Scheme 3), generated from cyclization of the aromatic rings with the isocyanate ions, were obtained with 26% and 16% yields respectively. For the ω-azido carboxylic acids **1d**-**1g**, the potential tricyclic lactam formation was not preferred, and the amides **3d**-**3g** was obtained with some better yields. Undoubtedly, the alkyl substituted substrates **1h** and **1i** were also successfully converted to the corresponding amides.

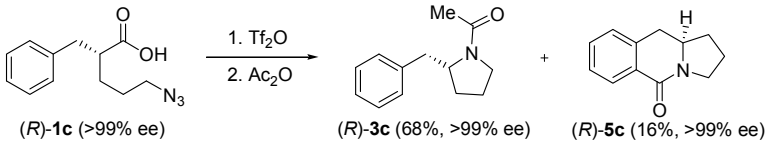


Scheme 3. Schmidt reaction of the 2-substituted ω-azido carboxylic acids

The Tf_2O-promoted Schmidt reaction of the 2-substituted ω-azido carboxylic acid mainly afforded the isocyanate ions as the initial products. As the experimental results, the isocyanate ion products were mainly hydrolyzed to the corresponding pyrrolidines, and the potential intramolecular addition of aromatic rings onto the isocyanate ions of the 2-aryl (**1a** and **1b**) and 2-benzyl (**1c**) substituted substrates did not dominate the following process. It should be noted that cyclization of the aromatic ring with the isocyanate ion had been furnished under the previous

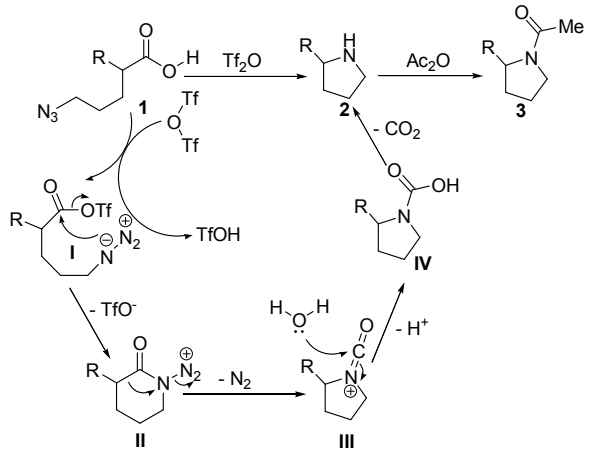
conditions.[4a,4c] In view of the whole conversion, the 2-substituted ω-azido carboxylic acids formally experienced a decarboxylation process, the denitrogenation of the azide, and the annulation for producing a pyrrolidine ring. The 2-substituted pyrrolidines could be found as the vast substructures in many natural products and pharmaceuticals,[7] and lots of synthetic strategies have been reported.[8]

Generally, the Schmidt reaction of alkyl azides is reported to be a stereospecific 1,2-migration process. To demonstrate it, an enantiomerically pure (*R*)-1c (>99% ee) was prepared[9] and submitted to the above experimental conditions (Scheme 4), affording the optically active amide (*R*)-**3c** (99% ee) and the tricyclic lactam (*R*)-**5c** (99% ee) with similar yields to that from the racemic **1c**, which indicated that the stereochemistry of the migration group was maintained during the rearrangement.



Scheme 4. Schmidt reaction of the enantiomerically pure (*R*)-**1c**

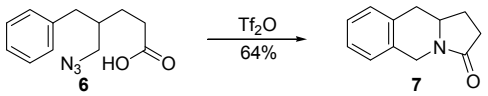
The above experimental results indicated that the Tf_2O could efficiently promote the Schmidt reaction of the 2-substituted ω-azido carboxylic acids. A possible mechanism of this conversion was proposed (Scheme 5). The formation of mixed anhydride **I** from the ω-azido carboxylic acid and Tf_2O with releasing a molecular TfOH was a necessary stage, and it initiated the Schmidt rearrangement process. An intramolecular attack of the azido group upon the carbonyl group of the mixed anhydride **I** resulted in forming the aminodiazonium ion intermediate **II**. Then a subsequent TfOH-promoted 1,2-migration of the more substituted carbon to the nitrogen atom gave the isocyanate ion **III**, which would be hydrolyzed to a carbamic acid **IV**. The unstable carbamic acid would smoothly decompose into the pyrrolidine **2** with releasing a molecular carbon dioxide gas. Finally, protection of the pyrrolidine with Ac_2O would give the 1-acetylpyrrolidine **3** as the ultimate product.



Scheme 5. The possible mechanism of the reaction of 2-substituted ω-azido carboxylic acid.

We have reported that the isocyanate ion and the *N*-acyliminium ion could be generated from Schmidt reaction of two different type of acyl chlorides. It could be expected that the 4-substituted ω-azido carboxylic acid would proceed through the *N*-acyliminium ion under the Tf_2O conditions. Then the 4-benzyl ω-azido carboxylic acid **6** was selected to see if the proposed Schmidt reaction

and the cyclization of the *N*-acyliminium ion with an aromatic ring could both proceed well under the above conditions. Fortunately, treatment of **6** with Tf_2O (4.0 equiv) at room temperature for 48h directly afforded the tricyclic lactam **7** in 64% yield (Scheme 6).



Scheme 6. Tf_2O-promoted Schmidt reaction of the 4-benzyl ω-azido carboxylic acid

In summary, we have designed and realized the Tf_2O-promoted Schmidt reaction of the ω-azido carboxylic acids, and the Tf_2O was employed as the initial activator for the carboxylic acid and the precursor of the acid promoter for the Schmidt reaction. A series of 2-substituted pyrrolidine were prepared through the hydrolysis of the isocyanate ions from the Schmidt reaction. One tricyclic lactam was produced from the 4-benzyl ω-azido carboxylic acid, where a further intramolecular cyclization of the *N*-acyliminium ion with the aromatic ring was addressed.

EXPERIMENTAL SECTION

All the reagents were purchased from *Acros*, *Sigma-Aldrich*, *Alfa-Aesar*, *aladdin*, *Accela* or *Adamas*, and they were used as received. All the solvents were distilled using the classic method before use. The reactions were monitored by the thin layer chromatography (TLC) on 2.5*10 cm, 250 μm analytical plates coated with silica gel 60 F254, and they were purchased from *Qingdao Haiyang Chemical Co. Ltd*. The thin layer chromatography plates were visualized by exposure to the ultraviolet light (UV, 254 nm) or Phosphomolybdic acid. Purification of the synthetic compounds by the flash column chromatography employed the neutral Silica gel (200-300 mesh or 300-400 mesh), which were purchased from *Qingdao Haiyang Chemical Co. Ltd*. The NMR spectra were recorded on a Bruker 400 MHz spectrometer, and the tetramethylsilane (δ = 0 and δ = 7.26) was used as an internal standard for ^{1}H NMR (400MHz) and $CDCl_3$ (δ = 77.16) for ^{13}C NMR(100 MHz), and the ^{13}C NMR were plus APT [methyl and methine (down), methylene and quaternary carbon (up)]. The IR spectra were recorded on a Perkein Elmer with potassium bromide crystal optic rectangle. High-resolution mass spectra (HRMS) were measured on a LTQ Orbitrap XL Domain 35A (Thermo Fisher) spectrometer, and the electro spray ionization (ESI) was used as the ion source. All the ω-azido carboxylic acids were prepared according to our previously reported procedure,[10] and **1a**, **1b** and **1c** had been previously prepared.[4a,4d] All the alkylation reactions and the Schmidt reactions were carried out in dry reaction vessels or flasks under a positive pressure of nitrogen or argon.

Diethyl 2-phenethylmalonate (9d). To a stirred suspension of NaH (60% in mineral oil, 880 mg, 22.0 mmol) in dry THF (73 mL) at room temperature was added a solution of diethyl malonate (3.52 g, 22.0 mmol) in THF (7 mL). The reaction mixture was kept for 1 h, then a solution of bromide **8d** (3.70 g, 20.0 mmol) in THF (7 mL) was added dropwise. The reaction mixture was heated to reflux for 23 h, then the mixture was cooled to room temperature, quenched with saturated NH_4Cl (15 mL), extracted with ethyl acetate (20 mL*3), and washed with brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give **9d** as a colorless oil (3.70g, 70%). **9d**, known compound[11]; R_f= 0.57, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.27-7.30 (m, 2 H), 7.18-7.23 (m, 3 H), 4.14-4.25 (m, 4 H), 3.32-3.36 (m, 1 H), 2.26 (t, *J* = 7.8 Hz, 2 H), 2.22 (q, *J* = 8.0 Hz, 2 H), 1.25-1.29(m, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.4 (2), 140.7, 61.4 (2), 33.3, 30.4, and down: 128.6 (2), 128.5 (2), 126.2, 51.3, 14.1 (2).

Diethyl 2-(2-chlorophenethyl)malonate (9e). The malonate **9e** (4.30 g) was prepared from diethyl malonate (3.52 g, 22.0 mmol) and bromide **8e** (4.39 g, 20.0 mmol) by the procedure for preparation of **9d**, and the yield was 71%. **9e**, R_f = 0.5, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (d, *J* = 7.6 Hz, 1 H), 7.12-7.23 (m, 3 H), 4.20 (q, J = 7.2 Hz, 4 H), 3.38 (t, *J* = 7.4 Hz, 1 H), 2.79 (t, *J* = 7.8 Hz, 2 H), 2.22 (q, J = 7.6 Hz, 2 H), 1.27 (t, *J* = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.2 (2), 138.3, 134.0, 61.4 (2), 31.1, 28.6, and down: 130.6, 129.6, 127.8, 126.9, 51.4, 14.1 (2); IR (film) 1749, 1731 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{19}ClO_4Na$ 321.0864, found 321.0867.

Diethyl 2-(3-chlorophenethyl)malonate (9f). The malonate **9f** (4.96 g) was prepared from diethyl malonate (3.52 g, 22.0 mmol) and bromide **8f** (4.39 g, 20.0 mmol) by the procedure for preparation of **9d**, and the yield was 83%. **9f**, R_f = 0.55, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17-7.24 (m, 3 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 4.20 (q, *J* = 7.2 Hz, 4 H), 3.33 (t, *J* = 7.4 Hz, 1 H), 2.64 (t, *J* = 7.8 Hz, 2 H), 2.20 (q, *J* = 7.8 Hz, 2 H), 1.27 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.2 (2), 142.7, 134.2, 61.5 (2), 33.0, 30.1, and down: 129.8, 128.7, 126.8, 126.4, 51.1, 14.1 (2); IR (film) 1749, 1732 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{19}ClO_4Na$ 321.0864, found 321.0861.

Diethyl 2-(4-chlorophenethyl)malonate (9g). The malonate **9g** (5.68 g) was prepared from diethyl malonate (3.52 g, 22.0 mmol) and bromide **8g** (4.39 g, 20.0 mmol) by the procedure for preparation of **9d**, and the yield was 95%. **9g**, R_f = 0.47, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23 (d, *J* = 8.4 Hz, 2 H), 7.11 (d, *J* = 8.4 Hz, 2 H), 4.13-4.25 (m, 4 H), 3.32 (t, *J* = 7.4 Hz, 1 H), 2.63 (t, *J* = 7.6 Hz, 2 H), 2.19 (q, *J* = 7.4 Hz, 2 H), 1.26 (t, *J* = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.0 (2), 139.1, 131.8, 61.3 (2), 32.5, 30.1, and down: 129.8 (2), 128.4 (2), 50.9, 14.0 (2); IR (film) 1750, 1732 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{15}H_{19}ClO_4Na$ 321.0864, found 321.0869.

Diethyl 2-cyclohexylmalonate (9h). The malonate **9h** (5.86 g) was prepared according to the literature: To a stirred suspension of KO^{t}Bu (4.03 g, 36.0 mmol) in DMSO (30 mL) was added diethyl malonate (4.80 g, 30.0 mmol) and iodocyclohexane (9.45g, 45.0 mmol). The mixture was heated to 80℃ for 6 h. Then the mixture was cooled to room temperature and quenched with H_2O (25 mL). The mixture was extracted with EA (10 mL * 3), and the combined organic phase was washed with brine (10 mL * 5), dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give **9h** a yellowish oil (5.86 g, 81% yield from the diethyl malonate). **9h**, known compound[12]; R_f = 0.62, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.15-4.22 (m, 4 H), 3.14 (d, *J* = 9.2 Hz, 1 H), 2.04-2.13 (m, 1 H), 1.64-1.73 (m, 5 H), 1.01-1.33 (m, 11 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 168.9 (2), 61.2 (2), 30.9 (2), 26.2, 26.1 (2), and down: 58.5, 38.0, 14.2 (2).

Diethyl 2-heptylmalonate (9i). The malonate **9i** (1.18 g) was prepared from diethyl malonate (1.76 g, 11.0 mmol) and bromide **8i** (2.26 g, 10.0 mmol) by the procedure for preparation of **9d**, and the yield was 46%. **9i**, known compound[13]; R_f = 0.55, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.19 (q, J = 7.0 Hz, 4 H), 3.31 (t, *J* = 7.6 Hz, 1 H), 1.86-1.91 (m, 2 H), 1.22-1.43 (m, 16 H), 0.87 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.8 (2), 61.4 (2), 31.9, 29.3, 29.1, 28.9, 27.5, 22.7, and down: 52.2, 14.2 (3).

Diethyl 2-(3-chloropropyl)-2-phenethylmalonate (10d). To a stirred suspension of NaH (60% in mineral oil, 560 mg, 14.0 mmol) in dry THF (40 mL) at room temperature was added a solution of malonate **9d** (3.70 g, 14.0 mmol) in THF (4 mL). The mixture was kept for 1 h, then a solution

of 1-chloro-3-iodopropane (2.61 g, 12.7 mmol) in THF (4 mL) was added. The mixture was kept for 22 h. Then the reaction was quenched by saturated NH_4Cl (10 mL), extracted with ethyl acetate (20 mL*3), and washed with brine (20 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give the chloride **10d** as a slightly yellow oil (3.45 g, 80% yield from the 1-chloro-3-iodopropane). **10d**, R_f = 0.55, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.31 (m, 2 H), 7.17-7.21 (m, 3 H), 4.20 (q, J = 7.0 Hz, 4 H), 3.54 (t, *J* = 6.2 Hz, 2 H), 2.50-2.55 (m, 2 H), 2.17-2.39 (m, 2 H), 2.09-2.13 (m, 2 H), 1.69-1.77 (m, 2 H), 2.17 (t, J = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.3 (2), 141.3, 61.4 (2), 57.1, 44.9, 34.6, 30.6, 30.2, 27.6, and down: 128.5 (2), 128.4 (2), 126.1, 14.2 (2); IR (film) 1729 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{25}ClO_4Na$ 363.1334, found 363.1333.

Diethyl 2-(2-chlorophenethyl)-2-(3-chloropropyl)malonate (10e). The chloride **10e** (3.90 g) was prepared from malonate **9e** (4.30 g, 14.4 mmol) and 1-chloro-3-iodopropane (2.68 g, 13.1 mmol) by the procedure for preparation of **10d**, and the yield was 79%. **10e**, R_f = 0.51, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (d, *J* = 7.2 Hz, 1 H), 7.12-7.23 (m, 3 H), 4.22 (q, *J* = 7.2 Hz, 4 H), 3.57 (t, *J* = 6.4 Hz, 2 H), 2.62-2.66 (m, 2 H), 2.13-2.18 (m, 4 H), 1.73-1.80 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.3 (2), 138.9, 133.9, 61.5 (2), 57.1, 44.9, 32.8, 30.0, 28.6, 27.6, and down: 130.6, 129.6, 127.8, 127.0, 14.2 (2); IR (film) 1728 cm^{-1}; IR(film) 1729 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{24}Cl_2O_4Na$ 397.0944, found 397.0950.

Diethyl 2-(3-chlorophenethyl)-2-(3-chloropropyl)malonate (10f). The chloride **10f** (4.98 g) was prepared from malonate **9f** (4.96 g, 16.6 mmol) and 1-chloro-3-iodopropane (3.09 g, 15.1 mmol) by the procedure for preparation of **10d**, and the yield was 88%. **10f**, R_f = 0.52, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17-7.27 (m, 3 H), 7.05 (d, *J* = 6.8 Hz, 1 H), 4.18-4.25 (m, 4 H), 3.54 (t, *J* = 6.4 Hz, 2 H), 2.50-2.54 (m, 2 H), 2.09-2.23 (m, 4 H), 1.68-1.77 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.2 (2), 143.4, 134.2, 61.5 (2), 57.0, 44.9, 34.4, 30.4, 30.3, 27.6, and down: 129.8, 128.5, 126.7, 126.4, 14.2 (2); IR (film) 1728 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{24}Cl_2O_4Na$ 397.0944, found 397.0948.

Diethyl 2-(4-chlorophenethyl)-2-(3-chloropropyl)malonate (10g). The chloride **10g** (4.66 g) was prepared from malonate **9g** (5.68 g, 19.0 mmol) and 1-chloro-3-iodopropane (3.54 g, 17.0 mmol) by the procedure for preparation of **10d**, and the yield was 72%. **10g**, R_f = 0.45, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.23-7.27 (m, 2 H), 7.10-7.12 (m, 2 H), 4.18-4.23 (m, 4 H), 3.55 (t, *J* = 6.4 Hz, 2 H), 2.48-2.52 (m, 2 H), 2.03-2.17 (m, 4 H), 1.67-1.76 (m, 2 H), 1.26-1.29 (m, 6 H);^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.2 (2), 139.8, 131.9, 61.5 (2), 57.0, 44.9, 34.6, 30.3, 30.1, 27.6, and down: 129.8 (2), 128.6 (2), 14.2 (2); IR (film) 1729 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{24}Cl_2O_4Na$ 397.0944, found 397.0945.

Diethyl 2-(3-chloropropyl)-2-cyclohexylmalonate (10h). The chloride **10h** (4.06 g) was prepared from malonate **9h** (5.86 g, 24.2 mmol) and 1-chloro-3-iodopropane (4.50 g, 22.0 mmol) by the procedure for preparation of **10d**, and the yield was 58%. **10h**, R_f = 0.65, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.19 (q, *J* = 7.0 Hz, 4 H), 3.51 (t, *J* = 6.4 Hz, 2 H), 1.91-2.06 (m, 3 H), 1.58-1.78 (m, 8 H), 1.27 (t, *J* = 7.0 Hz, 6 H), 0.98-1.18 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.0 (2), 61.2, 60.9 (2), 45.2, 31.0, 28.7 (2), 28.2, 27.0 (2), 26.5, and down: 42.7, 14.2 (2); IR (film) 1725 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{27}ClO_4Na$

341.1490, found 341.1492.

Diethyl 2-(3-chloropropyl)-2-heptylmalonate (10i). The chloride **10i** (332 mg) was prepared from malonate **9i** (714 mg, 2.7 mmol) and 1-chloro-3-iodopropane (511 mg, 2.50 mmol) by the procedure for preparation of **10d**, and the yield was 39%. **10i**, R_f = 0.57, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.19 (q, J = 7.0 Hz, 4 H), 3.53 (t, *J* = 6.2 Hz, 2 H), 1.99-2.05 (m, 2 H), 1.85-1.88 (m, 2 H), 1.64-1.71 (m, 2 H), 1.14-1.30 (m, 16 H), 0.87 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.6 (2), 61.2 (2), 57.1, 44.9, 32.4, 31.8, 29.8 (2), 29.0, 27.6, 23.9, 22.7, and down: 14.1 (3); IR (film) 1731 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{31}ClO_4Na$ 357.1803, found 357.1801.

Diethyl 2-(3-azidopropyl)-2-phenethylmalonate (11d). To a stirred solution of (3.45 g, 10.1 mmol) in DMF (30 mL) was added NaN_3 (1.31 g, 20.3 mmol) at room temperature. The mixture was kept at 50 ^{o}C for 48 h, then the resulting mixture was cooled to room temperature, and it was partitioned between ethyl acetate (60 mL) and H_2O (50 mL). The organic phase was separated and the aqueous phase was extracted with ethyl acetate (50 mL*3), then the combined extract was washed by water (15 mL*7), and brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give azide **11d** as a colorless oil (3.35 g, 95% yield from chloride **10d**). **11d**, R_f = 0.55, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.26-7.31 (m, 2 H), 7.17-7.22 (m, 3 H), 4.20 (q, *J* = 7.0 Hz, 4 H), 3.29 (t, *J* = 6.6 Hz, 2 H), 2.50-2.54 (m, 2 H), 2.17-2.21 (m, 2 H), 2.01-2.05 (m, 2 H), 1.50-1.57 (m, 2 H), 1.27 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.4 (2), 141.4, 61.5 (2), 57.3, 51.5, 34.7, 30.8, 30.1, 24.0, and down: 128.6 (2), 128.5 (2), 126.3, 14.3 (2); IR(film) 2098, 1729 cm^{-1}; IR (film) 2098, 1724cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{25}N_3O_4Na$ 370.1737, found 370.1732.

Diethyl 2-(3-azidopropyl)-2-(2-chlorophenethyl)malonate (11e). The azide **11e** (3.54 g) was prepared from malonate **10e** (3.90 g, 10.4 mmol) and sodium azide (2.03 g, 31.2 mmol) by the procedure for preparation of **11d**, and the yield was 89%. **11e**, R_f = 0.51, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.33 (d, *J* = 7.2 Hz, 1 H), 7.12-7.21 (m, 3 H), 4.22 (q, *J* = 7.2 Hz, 4 H), 3.32 (t, *J* = 6.8 Hz, 2 H), 2.61-2.66 (m, 2 H), 2.14-2.21 (m, 2 H), 2.05-2.09 (m, 2 H), 1.54-1.62 (m, 2 H), 1.28 (t, *J* = 7.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.1 (2), 138.8, 133.7, 61.4 (2), 57.0, 51.3, 32.7, 29.6, 28.5, 23.8, and down: 130.5, 129.5, 127.7, 126.9, 14.1 (2); IR(film) 2097, 1728 cm^{-1}; IR (film) 2932, 1724cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{24}ClN_3O_4Na$ 404.1348, found 404.1343.

Diethyl 2-(3-azidopropyl)-2-(3-chlorophenethyl)malonate (11f). The azide **11f** (4.06 g) was prepared from malonate **10f** (4.98 g, 13.2 mmol) and sodium azide (2.59 g, 39.8 mmol) by the procedure for preparation of **11d**, and the yield was 80%. **11f**, R_f = 0.52, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.17-7.27 (m, 3 H), 7.05 (d, *J* = 6.8 Hz, 1 H), 4.21 (q, *J* = 7.2 Hz, 4 H), 3.32 (t, *J* = 6.8 Hz, 2 H), 2.49-2.54 (m, 2 H), 2.15-2.23 (m, 2 H), 2.00-2.04 (m, 2 H), 1.50-1.57 (m, 2 H), 1.27 (t, *J* = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.2 (2), 143.3, 134.2, 61.5 (2), 57.1, 51.4, 34.5, 30.4, 30.1, 23.9, and down: 129.8, 128.5, 126.5, 126.4, 14.2 (2); IR (film) 2098, 1729 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{24}ClN_3O_4Na$ 404.1348, found 404.1347.

Diethyl 2-(3-azidopropyl)-2-(4-chlorophenethyl)malonate (11g). The azide **11g** (3.96 g) was prepared from malonate **10g** (4.66 g, 12.4 mmol) and sodium azide (2.42 g, 37.3 mmol) by the procedure for preparation of **11d**, and the yield was 84%. **11g**, R_f= 0.52, (EtOAC/PE = 1/5); ^{1}H

NMR ($CDCl_3$, 400 MHz) δ: 7.24 (d, *J* = 8.4 Hz, 2 H), 7.10 (d, *J* = 8.4 Hz, 2 H), 4.21 (q, *J* = 7.0 Hz, 4 H), 3.30 (t, *J* = 6.4 Hz, 2 H), 2.48-2.52 (m, 2 H), 2.13-2.17 (m, 2 H), 2.00-2.04 (m, 2 H), 1.50-1.57 (m, 2 H), 1.27 (t, *J* = 7.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.2 (2), 139.8, 131.9, 61.5 (2), 57.1, 51.4, 34.6, 30.1 (2), 23.3, and down: 129.8 (2), 128.6 (2), 14.2 (2); ^{13}C NMR (DMSO, 100 MHz, plus APT) δ, up: 170.7 (2), 140.3, 130.4, 61.2 (2), 56.6, 50.7, 33.9, 29.3, 29.1, 23.3, and down: 130.3 (2), 128.5 (2), 14.0 (2); IR (film) 2099, 1730 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{18}H_{24}ClN_3O_4Na$ 404.1348, found 404.1343.

Diethyl 2-(3-azidopropyl)-2-cyclohexylmalonate (11h). The azide **11h** (1.38 g) was prepared from malonate **10h** (2.03 g, 6.3 mmol) and sodium azide (1.24 g, 19.1 mmol) by the procedure for preparation of **11d**, and the yield was 67%. **11h**, R_f = 0.65, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.20 (q, *J* = 7.0 Hz, 4 H), 3.27 (t, *J* = 6.6 Hz, 2 H), 1.94 (t, *J* = 8.4 Hz, 3 H), 1.77 (d, *J* = 10.8 Hz, 4 H), 1.67 (d, *J* = 12.4 Hz, 1 H), 1.50-1.59 (m, 3 H), 1.27 (t, *J* = 7.0 Hz, 6 H), 1.02-1.22 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 170.9 (2), 61.2, 60.8 (2), 51.6, 30.7, 28.6 (2), 26.9 (2), 26.4, 24.4, and down: 42.7, 14.2 (2); IR (film) 2098, 1725 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{27}N_3O_4Na$ 348.1894, found 348.1894.

Diethyl 2-(3-azidopropyl)-2-heptylmalonate (11i). The azide **11i** (268 mg) was prepared from malonate **10i** (332 mg, 0.57 mmol) and sodium azide (193 mg, 3.0 mmol) by the procedure for preparation of **11d**, and the yield was 79%. **11i**, R_f = 0.53, (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.15 (q, *J* = 7.2 Hz, 4 H), 3.25 (t, *J* = 6.6 Hz, 2 H), 1.81-1.92 (m, 4 H), 1.41-1.49 (m, 2 H), 1.10-1.23 (m, 16 H), 0.84 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 171.6 (2), 61.2 (2), 57.2, 51.5, 32.5, 31.8, 29.8, 29.6, 29.1, 24.0, 23.9, 22.7, and down: 14.1 (3); IR (film) 2098, 1731 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{17}H_{31}N_3O_4Na$ 364.2207, found 364.2200.

5-Azido-2-phenylpentanoic acid (1a). The ω-azido carboxylic acid **1a** was previously prepared in our laboratory. **1a**, R_f = 0.55, (MTBE/1%NaH_2PO_4/AcOH/PE = 1/0.1/0.01/3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.16 (bs, 1 H), 7.27-7.36 (m, 5 H), 3.57 (t, *J* = 7.6 Hz, 1 H), 3.28 (t, *J* = 6.6 Hz, 2 H), 2.10-2.19 (m, 1 H), 1.83-1.93 (m, 1 H), 1.48-1.66 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 180.2, 137.9, 51.2, 30.1, 26.9, and down: 129.0 (2), 128.1 (2), 127.9, 51.2.

5-Azido-2-(naphthalen-1-yl)pentanoic acid (1b). The ω-azido carboxylic acid **1b** was previously prepared in our laboratory. **1b**, R_f = 0.53, (MTBE/1%NaH_2PO_4/AcOH/PE = 1/0.1/0.01/3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.08 (bs, 1 H), 8.10 (d, *J* = 8.4 Hz, 1 H), 7.88 (d, *J* = 7.6 Hz, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.44-7.58 (m, 4 H), 4.41 (t, *J* = 7.4Hz, 1 H), 3.29 (t, *J* = 6.8 Hz, 2 H), 2.22-2.37 (m, 1 H), 1.96-2.08 (m, 1 H), 1.53-1.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 180.4, 134.13, 134.09, 131.6, 51.2, 29.8, 27.1, and down: 129.2, 128.4, 126.7, 125.9, 125.6, 125.1, 123.0, 46.2.

5-Azido-2-benzylpentanoic acid (1c). The ω-azido carboxylic acid **1c** was previously prepared in our laboratory. **1c**, R_f = 0.50, (MTBE/1%NaH_2PO_4/AcOH/PE = 1/0.1/0.01/3); Daicel Shimadzu HPLC (Model: LC20AT) for ee determination of enantio-enriched (*R*)-**1c**[9] [>99% ee, Daicel OJ-H 0.46*25 cm, n-Hexane:i-PrOH 98:2, 1mL/min, 35°C, 4.4 Mpa, 254 nm, t_r (major) 30.2 min, t_r (minor) 31.8 min; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.44 (bs, 1 H), 7.27-7.31(m, 2 H), 7.20-7.24 (m, 1 H), 7.17-7.18 (m, 2 H), 3.26 (t, *J* = 6.2 Hz, 2 H), 2.99-3.04 (m, 1 H), 2.66-2.78 (m, 2 H), 1.54-1.75 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 181.7, 138.6, 51.2, 38.1, 28.6, 26.7, and down: 128.9 (2), 128.6 (2), 126.7, 47.0.

5-Azido-2-phenethylpentanoic acid (1d). The previous procedure for preparation of **1a** was

employed: To a stirred solution of the azide **11d** (3.35 g, 9.65 mmol) in MeOH (44 mL) was added 50% aqueous KOH (44 mL). The mixture was heated to 70 ^{o}C for 12 h, then it was cooled to room temperature, and acidified with aqueous HCl (2.0 M) to PH = 1 - 2. The mixture was extracted with CH_2Cl_2 (30 mL*3). The combined organic phase was dried over Na_2SO_4, concentrated to afford the crude dicarboxylic acid as a white solid (3.04 g). The above mixture (1.0 g) was dissolved in AcOH (14 mL) at room temperature, and kept at 160^{o}C for 12 h. Then the resulting mixture was cooled, and diluted with H_2O (20 mL). The mixture was extracted with DCM (25 mL*3), and the combined organic phase was washed by water (15 mL*5) and brine, dired over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give the ω-azido carboxylic acid **1d** as a colorless oil (580 mg, 70% yield for two steps from azide **11d**). **1d**, R_f = 0.50, (MTBE/1%NaH_2PO_4/AcOH/PE= 1/0.1/0.01/3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.38 (bs, 1 H),7.26-7.31 (m, 2 H), 7.18-7.21 (m, 3 H), 3.28 (t, *J* = 6.4 Hz, 2 H), 2.60-2.74 (m, 2 H), 2.37-2.47 (m, 1 H), 1.94-2.07 (m, 1 H), 1.57-1.85 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 182.5, 141.3, 51.2, 33.8, 33.5, 29.1, 26.7, and down: 128.53 (2) 128.52 (2), 126.2, 44.5; IR (film) 2098, 1705 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{17}N_3O_2Na$ 270.1213, found 270.1220.

5-Azido-2-(2-chlorophenethyl)pentanoic acid (1e). The previous procedure for preparation of **1a** was employed: To a stirred solution of azide **11e** (3.54 g, 9.27 mmol) in MeOH (42 mL) was added 50% aqueous KOH (42 mL). The mixture was heated to 70 ^{o}C for 16 h, then it was cooled to room temperature, and acidified with aqueous HCl (2.0 M) to PH to 1-2. The mixture was extracted with CH_2Cl_2 (30 mL*3). The combined organic phase was dried over Na_2SO_4, concentrated to afford the crude dicarboxylic acid as a white solid (2.73g). The crude dicarboxylic acid (2.73 g) was dissolved in AcOH (45 mL) at room temperature, and kept at 160^{o}C for 12 h. Then the resulting mixture was cooled, and diluted with H_2O (20 mL). The mixture was extracted with DCM (25 mL*3), and the combined organic phase was washed by water (15 mL*5) and brine, dired over anhydrous Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give the ω-azido carboxylic acid **1e** as a colorless oil (1.98 g, 76% yield from alcohol **11e**). **1e**, R_f = 0.43, (MTBE/1%NaH_2PO_4/AcOH/PE = 1/0.1/0.01/3); (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.67 (bs, 1 H),7.33 (d, *J* = 6.4 Hz, 1 H), 7.12-7.26 (m, 3 H), 3.29 (t, *J* = 6.0 Hz, 2 H), 2.72-2.87 (m, 2 H), 2.41-2.51 (m, 1 H), 1.93-2.04 (m, 1 H), 1.59-1.90 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 182.1, 138.9, 134.0, 51.3, 32.0, 31.4, 29.1, 26.7, and down: 130.6, 129.7, 127.8, 127.0, 44.6; IR (film) 2098, 1705 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{16}ClN_3O_2Na$ 304.0823, found 304.0825.

5-Azido-2-(3-chlorophenethyl)pentanoic acid (1f). The ω-azido carboxylic acid **1f** (2.85 g) was prepared from the azide **11f** (4.06 g, 10.6 mmol) by the procedure for preparation of **1e**, and the yield was 95%. **1f**, R_f= 0.45, (MTBE/1%NaH_2PO_4/AcOH/PE= 1/0.1/0.01/3); (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.90 (bs, 1 H), 7.09-7.18 (m, 3 H), 6.99 (d, *J* = 7.2 Hz, 1 H), 3.22 (t, *J* = 6.4 Hz, 2 H), 2.50-2.64 (m, 2 H), 2.30-2.39 (m, 1 H), 1.87-1.96 (m, 1 H), 1.50-1.76 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 181.9, 143.4, 134.4, 51.3, 33.6, 33.3, 29.2, 26.7, and down: 129.8, 128.7, 126.8, 126.5, 44.5; IR(film) 2098, 1705 cm^{-1}; IR (film) 2098, 1704 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{16}ClN_3O_2Na$ 304.0823, found 304.0825.

5-Azido-2-(4-chlorophenethyl)pentanoic acid (1g). The ω-azido carboxylic acid **1g** (1.92 g) was prepared from the azide **11g** (3.96 g, 10.3 mmol) by the procedure for preparation of **1e**, and the yield was 66%. **1g**, R_f = 0.44, (MTBE/1%NaH_2PO_4/AcOH/PE= 1/0.1/0.01/3); ^{1}H NMR

($CDCl_3$, 400 MHz) δ: 11.62 (bs, 1 H),7.25 (d, *J* = 8.0 Hz, 2 H), 7.11 (d, *J* = 8.4 Hz, 2 H), 3.29 (t, *J* = 6.2 Hz, 2 H), 2.57-2.69 (m, 2 H), 2.39-2.44 (m, 1 H), 1.96-2.03 (m, 1 H), 1.56-1.81 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 182.0, 139.7, 132.0, 51.3, 33.7, 33.0, 29.2, 26.7, and down: 129.9 (2), 128.7 (2), 44.4; IR(film) 2097, 1704 cm^{-1}; IR (film) 2098, 1704 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{16}ClN_3O_2Na$ 304.0823, found 304.0832.

5-**Azido-2-cyclohexylpentanoic acid (1h).** The ω-azido carboxylic acid **1h** (1.64 g) was prepared from the azide **11h** (1.38 g, 4.2 mmol) by the procedure for preparation of **1e**, and the yield was 62%. **1h**, R_f = 0.51, (MTBE/1%NaH_2PO_4/AcOH/PE= 1/0.1/0.01/3); (EtOAC/PE = 1/5); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.72 (bs, 1 H),3.29 (t, *J* = 5.6 Hz, 2 H), 2.16-2.24 (m, 1 H), 1.54-1.81 (m, 10 H), 0.95-1.30 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 182.3, 51.3, 31.0, 30.3 (2), 27.2, 26.3 (2), 26.1, and down: 51.5, 40.0; IR (film) 2097, 1703 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{11}H_{19}N_3O_2Na$ 248.1369, found 248.1370.

2-(3-Azidopropyl)nonanoic acid (1i). The ω-azido carboxylic acid **1i** (140 mg) was prepared from the azide **11i** (268 mg, 0.70 mmol) by the procedure for preparation of **1e**, and the yield was 76%. **1i**, R_f = 0.55, (MTBE/1%NaH_2PO_4/AcOH/PE= 1/0.1/0.01/3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.50 (bs, 1 H),3.30 (t, *J* = 6.0 Hz, 2 H), 2.32-2.39 (m, 1 H), 1.14-1.70 (m, 16 H), 0.88 (t, *J* = 6.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 182.8, 51.3, 32.3, 31.9, 29.6, 29.2, 29.1, 27.3, 26.8, 22.8, and down: 45.1, 14.2; IR (film) 2097, 1706 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{23}N_3O_2Na$ 264.1683, found 264.1687.

1-(2-Phenylpyrrolidin-1-yl)ethan-1-one (3a). To a stirred solution of 2-phenyl ω-azido carboxylic acid **1a** (109 mg, 0.50 mmol) in DCM (2.0 mL) was added Tf_2O (126 uL, 0.75 mmol) at room temperature and kept for 11 h. Then the mixture was concentrated and the crude was diluted in ethyl acetate (2 mL). Then the mixture was treated with 5% aqueous KOH (2 mL), and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (2 mL * 3), and washed with brine (2 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated to afford the crude product as a pale yellow oil. The crude mixture was dissolved in DCM (10 mL), and DMAP (73 mg, 0.60 mmol) and Ac_2O (151 uL, 3.00 mmol) were added. The mixture was kept for 6 h at room temperature, then it was washed with aqueous HCl (2.0 M, 2 mL). The organic phase was separated, and the aqueous phase was extracted with DCM (2 mL*2). The combined organic phase was washed with brine, dired over anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography to give **3a** as a pale yellow oil (76 mg, 80% yield from **1a**). **3a**, R_f= 0.20 (EA/PE = 1:1), known compound[6], about 1:0.4 rotamer mixture; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.13-7.35 (m, 5 H for the major rotamer and 5 H for the minor rotamer), 5.22 (d, *J* = 7.6 Hz, 1 H for the minor rotamer), 4.92 (d, *J* = 8.0 Hz, 1 H for the major rotamer), 3.58-3.77 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.36-2.41 (m, 1 H for the major rotamer), 2.22-2.25 (m, 1 H for the minor rotamer), 2.14 (s, 3 H for the minor rotamer), 1.83-1.98 (m, 6 H for the major rotamer and 3 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 170.2 (major rotamer), 169.1 (minor rotamer), 143.1 (major rotamer), 142.8 (minor rotamer), 48.3 (minor rotamer), 46.8 (major rotamer), 36.2 (major rotamer), 34.0 (minor rotamer), 23.5 (minor rotamer), 21.8 (major rotamer), and down: 128.7 (2, major rotamer), 128.2 (2, minor rotamer), 127.1 (major rotamer), 126.5 (minor rotamer), 125.3 (2, minor rotamer), 125.2 (2, major rotamer), 62.1 (major rotamer), 60.1 (minor rotamer), 22.7 (minor rotamer), 22.5 (major rotamer).

1-(2-(Naphthalen-1-yl)pyrrolidin-1-yl)ethan-1-one (3b) and

9,10,11,11a-tetrahydro-7H-benzo[g]pyrrolo[2,1-a]isoindol-7-one (5b). The amide **3b** (56 mg) was prepared from the azide **1b** (107 mg, 0.4 mmol) by the procedure for preparation of **1a**, and the yield was 56%. The tricyclic lactam **5b** (23 mg) was also produced in 26% yield from the Schmidt reaction. **5b**, known compound[4d], R_f = 0.32 (EtOAC/PE = 1/1); δ: 8.33 (d, *J* = 6.8 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.78 (d, *J* = 8.4 Hz, 1 H), 7.57 (t, *J* = 7.6 Hz, 1 H), 7.49 (t, *J* = 7.86 Hz, 1 H), 7.37 (d, *J* = 6.8 Hz, 1 H), 5.01-5.04 (m, 1 H), 3.95-4.02(m, 1 H), 3.71-3.80 (m, 1 H), 2.13-2.27 (m, 1 H), 1.87-2.10(m, 3 H). **3b**, R_f= 0.21 (EA/PE = 1:1), about 1:0.4 rotamer mixture; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 8.02 - 7.98 (m, 1 H for the major rotamer and 1 H for the minor rotamer), 7.90 (d, *J* = 7.6 Hz, 1 H for the major rotamer), 7.83 (d, *J* = 8.0 Hz, 1 H for the minor rotamer), 7.78 (d, *J* = 8.0 Hz, 1 H for the major rotamer), 7.71 (d, *J* = 8.0 Hz, 1 H for the minor rotamer), 7.36-7.59 (m, 3 H for the major rotamer and 3 H for the minor rotamer), 7.21-7.26 (m, 1 H for the major rotamer), 7.10 (d, *J* = 8.0 Hz,1 H for the minor rotamer), 5.98 (d, *J* = 8.0 Hz, 1 H for the minor rotamer), 5.66 (d, *J* = 8.0 Hz, 1 H for the major rotamer), 3.85-3.93 (m, 1 H for the major rotamer and 1 H for the minor rotamer), 3.65-3.76 (m, 1 H for the major rotamer and 1 H for the minor rotamer), 2.48-2.58 (m, 1 H for the major rotamer), 2.36-2.41 (m, 1 H for the minor rotamer), 2.22 (s, 3 H for the minor rotamer), 1.84-2.07 (m, 6 H for the major rotamer and 3 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 170.4 (major rotamer), 169.3 (minor rotamer), 137.8 (major rotamer), 137.6 (minor rotamer), 134.2 (minor rotamer), 134.0 (major rotamer), 130.2 (minor rotamer), 129.9 (major rotamer), 48.6 (minor rotamer), 47.1 (major rotamer), 34.6 (major rotamer), 32.9 (minor rotamer), 23.7 (minor rotamer), 22.1(major rotamer), and down: 129.2 (major rotamer), 128.9 (minor rotamer), 128.0 (major rotamer), 127.4 (minor rotamer), 126.4 (major rotamer), 125.9 (major rotamer), 125.8 (minor rotamer), 125.5 (minor rotamer), 125.4 (major rotamer), 125.2 (minor rotamer), 123.5 (minor rotamer), 122.6 (major rotamer), 122.4 (major rotamer), 121.4 (minor rotamer), 59.5 (major rotamer), 57.8 (minor rotamer), 22.9 (minor rotamer), 22.5 (major rotamer); IR (film) 1640 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{16}H_{17}NONa$ 262.1202, found 262.1203.

1-(2-Benzylpyrrolidin-1-yl)ethan-1-one (3c) and 2,3,10,10a-tetrahydropyrrolo[1,2-b]isoquinolin-5(1H)-one (5c). The amide **3c** (71 mg) was prepared from the azide **1c** (116 mg, 0.5 mmol) by the procedure for preparation of **1a**, and the yield was 71%. The tricyclic lactam **5c** (16 mg) was also produced in 16% yield from the Schmidt reaction. **5c**, known compound[4a], R_f = 0.30 (EtOAC/PE = 1/1); Daicel Shimadzu HPLC (Model: LC20AT) for ee determination of enantio-enriched (*R*)-**3c** [99% ee, Daicel AD-H 0.46*25 cm, n-Hexane:i-PrOH 96:4, 1mL/min, 35°C, 3.4 Mpa, 254 nm, t_r (major) 16.0 min, t_r (minor) 17.3 min; ^{1}H NMR (CDCl3 , 400 MHz) δ: 8.04 (dd, *J* = 1.2 Hz and 7.6 Hz, 1 H), 7.37-7.41 (m, 1 H), 7.31-7.35 (m, 1 H), 7.17 (d, *J* = 7.6 Hz, 1 H), 3.75-3.87 (m, 2 H), 3.59-3.67 (m, 1 H), 3.02 (dd, *J* = 4.0 Hz and 15.2 Hz, 1 H), 2.82 (t, *J* = 14.2 Hz, 1 H), 2.24-2.32 (m, 1 H), 2.09-2.13 (m, 1 H), 1.67-1.92 (m, 2 H). **3c**, R_f= 0.19 (EA/PE = 1:1), about 1:0.5 rotamer mixture; Daicel Shimadzu HPLC (Model: LC20AT) for ee determination of enantio-enriched (*R*)-**3c** [99% ee, Daicel AD-H 0.46*25 cm, n-Hexane:i-PrOH 98:2, 1mL/min, 35°C, 3.2 Mpa, 254 nm, t_r (major 1) 29.9 min, t_r (major 2) 42.3 min, t_r (minor 1) 32.0 min, t_r (minor 1) 48.6 min; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.14-7.32 (m, 5 H for the major rotamer and 5 H for the minor rotamer), 4.29-4.32 (m, 1 H for the major rotamer), 3.99-4.03 (m, 1 H for the minor rotamer), 3.44-3.57 (m, 2 H for the minor rotamer), 3.31-3.41 (m, 2 H for the major rotamer), 3.17 (dd , *J* = 3.2 Hz and 13.2 Hz , 1 H for the major rotamer), 2.85 (dd, J = 5.6 Hz and 13.6 Hz, 1 H for the minor rotamer), 2.65 (q, J = 8.8 Hz,

1 H for the minor rotamer), 2.58 (dd , J = 9.2 Hz and 12.0 Hz, 1 H for the major rotamer), 2.07 (s, 3 H for the major rotamer), 1.96 (s, 3 H for the minor rotamer), 1.70-1.91 (m, 4 H for the major rotamer and 4 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.1 (major rotamer), 169.0 (minor rotamer), 139.0 (major rotamer), 137.9 (minor rotamer), 47.9 (major rotamer), 45.3 (minor rotamer), 40.7 (minor rotamer), 38.6 (major rotamer), 29.9 (minor rotamer), 28.2 (major rotamer), 23.5 (major rotamer), 21.6 (minor rotamer), and down: 129.4 (2, major rotamer), 129.1 (2, minor rotamer), 128.6 (2, minor rotamer), 128.1 (2, major rotamer), 126.6 (minor rotamer), 126.1 (major rotamer), 60.3 (minor rotamer), 58.2 (major rotamer), 23.0 (major rotamer), 21.9 (minor rotamer); IR (film) 1637 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{17}NONa$ 226.1202, found 226.1203.

1-(2-Phenethylpyrrolidin-1-yl)ethan-1-one (3d). The amide **3d** (73 mg) was prepared from the azide **1d** (123 mg, 0.5 mmol) by the procedure for preparation of **1a**, and the yield was 67%. **3d**, R_f = 0.23 (EA/PE = 1:1), known compound[14], about 1:0.5 rotamer mixture; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.05-7.27 (m, 5 H for the major rotamer and 5 H for the minor rotamer), 4.14 (bs, 1 H for the major rotamer), 3.75 (bs, 1 H for the minor rotamer), 3.37-3.58 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.51-2.72 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.13-2.21 (m, 1 H for the major rotamer and 1 H for the minor rotamer), 1.50-2.13 (m, 8 H for the major rotamer and 8 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.1 (major rotamer), 169.0 (minor rotamer), 141.9 (major rotamer), 140.8 (minor rotamer), 47.6 (major rotamer), 45.3 (minor rotamer), 36.3 (minor rotamer), 34.8 (major rotamer), 32.68 (major rotamer), 32.65 (minor rotamer), 30.1 (minor rotamer), 29.3 (major rotamer), 24.0 (major rotamer), 22.2 (minor rotamer), and down: 128.5 (2, minor rotamer), 128.27 (2, major rotamer), 128.25 (2, minor rotamer), 128.23 (2, minor rotamer), 126.2 (minor rotamer), 125.7 (major rotamer), 57.8 (minor rotamer), 56.8 (major rotamer), 23.0 (major rotamer), 21.9 (minor rotamer).

1-(2-(2-Chlorophenethyl)pyrrolidin-1-yl)ethan-1-one (3e). The amide **3e** (74 mg) was prepared from the azide **1e** (112 mg, 0.4 mmol) by the procedure for preparation of **1a**, and the yield was 74%. **3e**, R_f= 0.25 (EA/PE = 1:1), about 1:0.6 rotamer mixture; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.19-7.25 (m, 2 H for the major rotamer and 1 H for the minor rotamer), 6.99-7.10 (m, 2 H for the major rotamer and 3 H for the minor rotamer), 4.06 (bs, 1 H for the major rotamer), 3.69 (bs, 1 H for the minor rotamer), 3.22-3.46 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.56-2.72 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 1.98-2.09 (m, 1 H for the major rotamer and 1 H for the minor rotamer), 1.44-1.93 (m, 8 H for the major rotamer and 8 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 168.9 (major rotamer), 168.7 (minor rotamer), 139.2 (major rotamer), 138.3 (minor rotamer), 133.5 (major rotamer and minor rotamer), 47.4 (major rotamer), 45.2 (minor rotamer), 34.6 (minor rotamer), 32.9 (major rotamer), 30.4 (minor rotamer), 30.2 (major rotamer), 30.0 (minor rotamer), 29.1 (major rotamer), 23.8 (major rotamer), 22.0 (minor rotamer), and down: 130.11 (minor rotamer), 130.05 (major rotamer), 129.4 (minor rotamer), 129.0 (major rotamer), 127.5 (minor rotamer), 127.0 (major rotamer), 126.8 (minor rotamer), 126.6 (major rotamer), 57.8 (minor rotamer), 56.6 (major rotamer), 22.8 (major rotamer), 21.7 (minor rotamer); IR (film) 1635 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{18}ClNONa$ 274.0969, found 274.0969.

1-(2-(3-Chlorophenethyl)pyrrolidin-1-yl)ethan-1-one (3f). The amide **3f** (77 mg) was prepared from the azide **1f** (112 mg, 0.4 mmol) by the procedure for preparation of **1a**, and the

yield was 76%. **3f**, R_f= 0.27 (EA/PE = 1:1), about 1:0.5 rotamer mixture; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.96-7.16 (m, 4 H for the major rotamer and 4 H for the minor rotamer), 4.04 (bs, 1 H for the major rotamer), 3.66 (bs, 1 H for the minor rotamer), 3.23-3.46 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.45-2.62 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.11 - 2.02 (m, 1 H for the major rotamer and 1H for the minor rotamer), 1.41-1.93 (m, 8 H for the major rotamer and 8 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.2 (major rotamer), 168.9 (minor rotamer), 143.9 (major rotamer), 142.9 (minor rotamer), 134.2 (minor rotamer), 133.8 (major rotamer), 47.6 (major rotamer), 45.3 (minor rotamer), 36.0 (minor rotamer), 34.6 (major rotamer), 32.32 (major rotamer), 32.28 (minor rotamer), 30.1 (minor rotamer), 29.3 (major rotamer), 24.0 (major rotamer), 22.1 (minor rotamer), and down: 129.8 (minor rotamer), 129.5 (major rotamer), 128.3 (major rotamer and minor rotamer), 126.5 (major rotamer), 126.4 (minor rotamer), 126.3 (minor rotamer), 125.8 (major rotamer), 57.7 (minor rotamer), 56.6 (major rotamer), 22.9 (major rotamer), 21.9 (minor rotamer); IR (film) 1638 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{18}ClNONa$ 274.0969, found 274.0968.

1-(2-(4-Chlorophenethyl)pyrrolidin-1-yl)ethan-1-one (3g). The amide **3g** (77 mg) was prepared from the azide **1g** (112 mg, 0.4 mmol) by the procedure for preparation of **1a**, and the yield was 76%. **3g**, R_f = 0.28 (EA/PE = 1:1), about 1:0.5 rotamer mixture; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 6.99-7.26 (m, 4 H for the major rotamer and 4 H for the minor rotamer), 4.0 (bs, 1 H for the major rotamer), 3.64 (bs, 1 H for the minor rotamer), 3.25-3.44 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.40-2.59 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.02-2.09 (m, 1 H for the major rotamer and 1 H for the minor rotamer), 1.39-1.92 (m, 8 H for the major rotamer and 8 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 169.0 (major rotamer), 168.8 (minor rotamer), 140.2 (major rotamer), 139.2 (minor rotamer), 131.6 (minor rotamer), 131.1 (major rotamer), 47.4 (major rotamer), 45.2 (minor rotamer), 36.0 (minor rotamer), 34.5 (major rotamer), 31.8 (major rotamer and minor rotamer), 29.9 (minor rotamer), 29.2 (major rotamer), 23.8 (major rotamer), 22.0 (minor rotamer), and down: 129.5 (2, major rotamer), 129.4 (2, minor rotamer), 128.4 (2, minor rotamer), 128.1 (2, major rotamer), 57.5 (minor rotamer), 56.5 (major rotamer), 22.8 (major rotamer), 21.8 (minor rotamer); IR (film) 1635 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{14}H_{18}ClNONa$ 274.0969, found 274.0970.

1-(2-Cyclohexylpyrrolidin-1-yl)ethanone (**3h**). The amide **3h** (47 mg) was prepared from the azide **1h** (112 mg, 0.5 mmol) by the procedure for preparation of **1a**, and the yield was 49%. **3h**, R_f= 0.24 (EA/PE=1:1), about 1:0.5 rotamer mixture; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.5 (bs, 1 H for the major rotamer), 3.65-3.70 (m,1 H for the minor rotamer), 3.58 (bs,1 H for the minor rotamer), 3.27-3.40 (m, 2 H for the major rotamer), 3.18 (bs, 1 H for the minor rotamer), 2.02 (s, 3 H for the minor rotamer), 1.98 (s, 3 H for the major rotamer), 1.35-1.84 (m, 10 H for the major rotamer and 10 H for the minor rotamer), 0.81-1.18 (m, 5 H for the major rotamer and 5 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 174.2 (minor rotamer), 169.5 (major rotamer), 48.2 (major rotamer), 45.6 (minor rotamer), 30.3 (minor rotamer), 30.1 (major rotamer), 28.2 (minor rotamer), 27.8 (major rotamer), 27.5 (minor rotamer), 26.6 (major rotamer), 26.5 (minor rotamer), 26.4 (major rotamer and minor rotamer), 26.3 (minor rotamer), 26.2 (major rotamer), 26.1 (major rotamer), 24.6 (major rotamer), 22.9 (minor rotamer), and down: 63.5 (minor rotamer), 61.4 (major rotamer), 42.4 (minor rotamer), 40.0 (major rotamer), 23.3 (major rotamer), 22.4 (minor rotamer); IR (film) 1645 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{12}H_{21}NONa$ 218.1515, found 218.1516.

1-(2-Heptylpyrrolidin-1-yl)ethanone (3i). The amide **3i** (72 mg) was prepared from the azide **1i** (120 mg, 0.5 mmol) by the procedure for preparation of **1a**, and the yield was 68%. **3i**, R_f= 0.27 (EA/PE = 1:1), about 1:0.7 rotamer mixture; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.04 (bs, 1 H for the major rotamer), 3.74 (bs, 1 H for the minor rotamer), 3.33-3.55 (m, 2 H for the major rotamer and 2 H for the minor rotamer), 2.08 (s, 3 H for the minor rotamer), 2.02 (s, 3 H for the major rotamer), 1.68-1.99 (m, 6 H for the major rotamer and 6 H for the minor rotamer), 1.26 (bs, 10 H for the major rotamer and 10 H for the minor rotamer), 0.85-0.89 (m, 3 H for the major rotamer and 3 H for the minor rotamer); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up:168.8 (major rotamer and minor rotamer), 47.5 (major rotamer), 45.2 (minor rotamer), 34.8 (minor rotamer), 33.1 (major rotamer), 31.7 (major rotamer), 31.6 (minor rotamer), 30.1 (minor rotamer), 29.5 (major rotamer), 29.4 (minor rotamer), 29.2 (major rotamer), 29.13 (minor rotamer), 29.07 (major rotamer), 26.4 (minor rotamer), 26.3 (major rotamer), 23.9 (major rotamer), 22.53 (major rotamer), 22.50 (minor rotamer), 22.1 (major rotamer), and down: 58.6 (minor rotamer), 57.0 (major rotamer), 22.9 (major rotamer), 22.0 (minor rotamer), 14.0 (major rotamer and minor rotamer); IR (film) 1646 cm^{-1}; HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{13}H_{25}NONa$ 234.1828, found 234.1826.

2-Phenyl-1-((trifluoromethyl)sulfonyl)pyrrolidine (4a). To a stirred solution of 2-phenyl ω-azido carboxylic acid **1a** (129 mg, 0.6 mmol) in DCM (2 mL) was added Tf_2O (677 mg, 2.4 mmol). The mixture was kept at room temperature for 12 h. Then it was quenched by KOH (50%, 1 mL) and the mixture was kept at room temperature for an additional 1 h. The organic phase was separated and the aqueous phase was extracted by DCM (10 mL * 4). The combined organic phase was dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to afford triflamide **4a** as a colorless solid (108 mg, 64% yield from **1a**). **4a**, known compound[15]; R_f = 0.62 (EtOAC/PE = 1/10); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.31-7.35 (m, 2 H), 7.21-7.27 (m, 3 H), 5.07-5.11 (m, 1 H), 3.73-3.80 (m, 2 H), 2.31-2.46 (m, 1 H), 1.89-2.07 (m, 3 H) ; ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ, up: 141.5, 50.3, 35.9, 24.0, and down: 128.6 (2), 127.7, 125.8 (2), 64.8.

5-Azido-4-benzylpentanoic acid (6). The ω-azido carboxylic acid **6** was previously prepared in our laboratory.[4b] **6**, R_f = 0.52, (MTBE/1%NaH_2PO_4/AcOH/PE= 1/0.1/0.01/3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 10.99 (bs, 1 H), 7.29-7.32 (m, 2 H), 7.19-7.24 (m, 1 H), 7.15-7.17 (m, 2 H), 3.29 (dd, *J* = 12.4 Hz and 5.0 Hz, 1 H), 3.22 (dd, *J* = 12.4 Hz and 5.2 Hz, 1 H), 2.57-2.72 (m, 2 H), 2.40-2.45 (m, 2 H), 1.87-1.97 (m, 1 H), 1.67-1.82 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 179.0, 139.3, 53.8, 38.1, 31.5, 26.8, and down: 129.3 (2), 128.7 (2), 126.5, 39.6.

1,5,10,10a-Tetrahydropyrrolo[1,2-b]isoquinolin-3(2H)-one (7). To a stirred solution of the 4-benzyl ω-azido carboxylic acid **6** (163 mg, 0.7 mmol) in DCM (2 mL) was added Tf_2O (789 mg, 2.8 mmol). The mixture was kept at room temperature for 48 h. Then it was quenched by the addition of water (1 mL) and aqueous KOH (50%, 1 mL), and the mixture was stirred at room temperature for an additional 1 h. The organic phase was separated and the aqueous phase was extracted by DCM (10 mL * 4). The combined organic layers were dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to afford the desired lactams **7** as a colorless solid (84 mg, 64% yield from 4-benzyl ω-azido carboxylic acid **6**). **7**, known compound[4b]; R_f = 0.23 (EtOAC/PE = 2/1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.07-7.25 (m, 4 H), 4.92 (d, *J* = 17.6 Hz, 1 H), 4.25 (d, *J* = 17.6 Hz, 1 H), 3.74-3.90 (m, 1 H), 2.95 (dd, *J* = 15.6 Hz and *J* = 4.0 Hz, 1 H), 2.68 (dd, *J* = 15.6 Hz and 11.2 Hz, 1 H), 2.33-2.52 (m, 3 H), 1.75-1.86 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100 MHz, plus APT) δ up: 174.2, 133.2, 131.7, 42.5, 36.8, 30.1, 25.2, and down: 129.1, 126.7, 126.60, 126.56, 53.9.

ACKNOWLEDGMENT

This work was supported by the National Natural Science Foundation of China (No 21662027), and the Program for Leading Talents of Ningxia Province (KJT2015002).

SUPPORTING INFORMATION

The Supporting Information (copies of NMR spectra for all new compounds and X-ray crystallographic data for **4a**) is available free of charge on the ACS Publications website

References

1. For several selected reviews, see: (a) Wrobleski, A.; Coombs, T. C.; Huh, C. W.; Li, S.-W.; Aubé, J. *Org. React.* **2012**, *78*, 1–320; (b) Wolff, H. *Org. React.* **2011**, *3 (8)*, 307–336; (c) Aubé, J. In *Organic Azides: Synthesis and Applications*; Eds: Bräse, S., Banert, K.; Wiley: Weinheim, **2010**; pp 191–237. (d) Lang, S.; Murphy, J. A. Azide rearrangements in electron-deficient systems. *Chem. Soc. Rev.* **2006**, *35*, 146–156.
2. Schmidt reaction of alkyl azides with ketones, see: (a) Aubé, J.; Milligan, G. L. Intramolecular Schmidt Reaction of Alkyl Azides. *J. Am. Chem. Soc.* **1991**, *113*, 8965–8966. (b) Gracias, V.; Milligan, G. L.; Aubé, J. Efficient Nitrogen Ring-Expansion Process Facilitated by in Situ Hemiketal Formation. An Asymmetric Schmidt Reaction. *J. Am. Chem. Soc.* **1995**, *117*, 8047–8048. (c) Desai, P.; Schildknegt, K.; Agrios, K.; Mossman, A. C. J.; Milligan, G. L.; Aubé, J. Reactions of Alkyl Azides and Ketones as Mediated by Lewis Acids: Schmidt and Mannich Reactions Using Azide Precursors. *J. Am. Chem. Soc.* **2000**, *122*, 7226–7232. (d) Katz, C. E.; Aubé, J. Unusual Tethering Effects in the Schmidt Reaction of Hydroxyalkyl Azides with Ketones: Cation-π and Steric Stabilization of a Pseudoaxial Phenyl Group. *J. Am. Chem. Soc.* **2003**, *125*, 13948–13949. (e) Sahasrabudhe, K.; Gracias, V.; Fumess, K.; Sminth, B. T.; Katz, C. E.; Reddy, D. S.; Aubé, J. Asymmetric Schmidt Reaction of Hydroxyalkyl Azides with Ketones. *J. Am. Chem. Soc.* **2003**, *125*, 7914–7922.
3. Schmidt reaction of alkyl azides with aldehydes, see: (a) Badiang, J. G.; Aubé, J. One-Step Conversion of Aldehydes to Oxazolines and 5,6-Dihydro-4H-1,3-oxazines Using 1,2- and 1,3-Azido Alcohols. *J. Org. Chem.* **1996**, *61*, 2484–2487. (b) Lee, H.-L.; Aubé, J. Intramolecular and intermolecular Schmidt reactions of alkyl azides with aldehydes. *Tetrahedron*. **2007**, *63*, 9007–9015. (c) Gu, P.; Sun, J.; Kang, X.-Y.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. A Formal Metal-Free N-Arylation via the Schmidt Reaction of Aromatic Aldehydes with an Azido Amine. *Org. Lett*. **2013**, *15*, 1124–1127.
4. *in situ* activation strategy for the Schmidt reaction of alkyl azides with carboxylic acids in our group, see: (a) Gu, P. -M.; Kang, X.-Y.; Sun, J.; Wang, B.-J.; Yi, M.; Li, X.-Q.; Xue, P.; Li, R. Intramolecular Schmidt Reaction of Acyl Chlorides with Alkyl Azides: Rapid Access to Fused Polycyclic Nitrogen-Containing Heterocycles via a Multistep One-Pot Transformation. *Org. Lett.* **2012**, *14*, 5796–5799. (b) Li, X.-J.; Qiao, J.-B.; Sun, J.; Li, X.-Q.; Gu, P. Intramolecular Schmidt Reaction of Acyl Chlorides with Alkyl Azides: Capture of N-Acyliminium Ion Intermediates with Aromatic rings. *Org. Lett.* **2014**, *16*, 2865–2867. (c) Wang, B.-J.; Xue, P.; Gu, P. Intramolecular Schmidt Reaction of Acyl Chlorides with Alkyl Azides: Preparation of Pyrrolizine by Intramolecular Capture of Intermediates with Alkene or Alkyne. *Chem. Commun.* **2015**, *51*, 2277–2279. (d) Li, Q.-F.;

Li, R.; Li, X.-Q.; Gu, P. Preparation of Aryl Fused Pyrrolizidines via Intramolecular Schmidt Reaction of Acyl Chlorides with Alkyl Azides. *Chin. J. Org. Chem.* **2015**, *35*, 2326–2332.

5. For a recent example, see: Komiya, C.; Aihara, K.; Morishita, K.; Ding, H.; Inokuma, T.; Shigenaga, A.; Otaka, A. Development of an intein-inspired amide cleavage chemical device. *J. Org. Chem.* **2016**, *81*, 699–707.
6. Known compound, see: Wrobleski, A.; Aubé, J. Intramolecular Reactions of Benzylic Azides with Ketones: Competition between Schmidt and Mannich Pathways. *J. Org. Chem.* **2001**, *66*, 886–889.
7. For natural products, see: (a) Plunkett, A. O. Pyrrole, Pyrrolidine, Pyridine, Piperidine, and Azepine Alkaloids. *Nat. Prod. Rep.* **1994**, *11*, 581–590. (b) Pinder, A. R. Azetidine, Pyrrole, Pyrrolidine, Piperidine, and Pyridine Alkaloids. *Nat. Prod. Rep.* **1992**, *9*, 491–504.
8. For two recent examples for preparation of the 2-substituted pyrrolidine, see: (a) Munnuri, S.; Adebesin, A. M.; Paudyal, M. P.; Yousufuddin, M.; Dalipe, A.; Falck, J. R. Catalyst-Controlled Diastereoselective Synthesis of Cyclic Amines via C-H Functionalization. *J. Am. Chem. Soc.* **2017**, *139*, 18288–18294. (b) Zhu, N.; Wang, T.; Ge, L.; Li, Y.; Zhang, X.; Bao, H. γ-Amino Butyric Acid (GABA) Synthesis Enabled by Copper-Catalyzed Carboamination of Alkenes. *Org. Lett.* **2017**, *19*, 4718–4721.
9. Known compound, preparation according to our previously reported procedure, see: Li, X.-J.; Wang, B.-J.; Kang, X.-Y.; Gu, P.-M.; Li, X.-Q. Synthesis of (*R*)-benzoindolizidine by Intramolecular Schmidt Reaction of ω-Azido Acyl Chloride. *Chin. J. Synth. Chem.*, **2014**, *22*, 647–650.
10. The general synthetic method for the ω-azido carboxylic acids **1** is included in the supporting information.
11. Wu, Z.-X.; Minhas, G. S.; Wen, D.; Jiang, H.-L.; Chen, K.-X.; Zimniak, P.; Zheng, J. Design, Synthesis, and Structure-Activity Relationships of Haloenol Lactones: Site-Directed and Isozyme-Selective Glutathione S-Transferase Inhibitors. *J. Med. Chem.* **2004**, *47*, 3282–3294.
12. Puente, A.; He, S. -S.; Corral-Bautista, F.; Ofial, A. R.; Mayr, H. Nucleophilic Reactivities of 2-Substituted Malonates. *Eur. J. Org. Chem.* **2016**, 1841–1848.
13. Chilmonczyk, Z.; Sienicki, Ł.; Łozowicka, B.; Lisowska-Kuźmicz, M.; Jończyk, A.; AboulEnein, H. Y. Structure-Retention Relationship in a Series of Chiral 1,4-Disubstituted Piperazine Derivatives on Carbohydrate Chiral Stationary Phases. *Farmaco*, **2005**, *60*, 439–443.
14. Slater, K. A.; Friestad, G. K. Mn-Mediated Radical-Ionic Annulations of Chiral N-Acylhydrazones. *J. Org. Chem.* **2015**, *80*, 6432–6440.
15. Togo, H.; Hoshina, Y.; Muraki, T.; Nakayama, H.; Yokoyama, M. Study on Radical Amidation onto Aromatic Rings with (Diacyloxyiodo)arenes. *J. Org. Chem.* **1998**, *63*, 5193–5200.