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Lewis acid-mediated azidolysis of 2,3-three membered heterocyclic amines

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ABSTRACT

The Lewis acid-catalyzed regioselective azidolysis of 2,3-three membered heterocyclic amines has been investigated. The results obtained demonstrated that using $TMSN_3$ as a source of azide, the appropriate choice of Lewis acid allowed to obtain different regio- and stereocontrolled precursors of aminoalcoholic and triaminic sequences. Considering the occurrence of these moieties in the structure of many biologically active compounds, the present methodologies could represent a powerful tool in organic synthesis for the preparation of interesting molecules.

1. Introduction

Epoxides and aziridines are among the most versatile classes of compounds in organic chemistry on the basis of their facile nucleophilic ring opening, which generally occurs with inversion of configuration at the reacting carbon atom, as expected in a S_N2-pathway.[1] This reactivity has allowed the easy access to a broad range of 1,2-difunctionalized organic compounds with two stereocontrolled contiguous chiral centers. In this contest, in the last years, our considerable research interest has been focused on the regio- and stereoselective opening of 2-functionalized epoxides and aziridines, mainly by means of metal halides.[2] More recently, our attention turned to the use of azide as the nucleophile,[3] one of the most popular amine precursors, and connected with a project aimed at the synthesis of new peptidomimetics as enzyme inhibitors,[4] 2,3-three membered heterocyclic amines were considered the substrates suitable for our purpose. Their ring opening would provide diaminoalcohols and triamino fragments, moieties recurrent in many peptidomimetic protease inhibitors, such as HIV protease,[5] renine,[6] γ-secretase,[7] human β-secretase (BACE1),[8] malarial plasmepsins I and II,[9] and in [1,4]-benzodiazepines,[10] but also widespread in natural products, such as (−)-balanol,[11] and its regioisomer ophiocordin[12] (Fig. 1).

The 2,3-three epoxy amines were synthesized in satisfactory yield from the corresponding allylic alcohols through the sequence described below: (a) epoxidation of allylic alcohol, (b) transformation of the hydroxyl function into a good leaving group such as the mesylate, (c) nucleophilic substitution with an amine (Scheme 1).

Recently, we have briefly reported a Lewis acid-mediated regioselective azidolysis of 2,3-epoxy amines,[13] using $TMSN_3$ as the source of azide in the presence of three different Lewis acids: $BF_3 \cdot OEt_2$ (method A), $ZnCl_2$ (method B), and Ti(O-*i*-Pr)$_4$ (method C), which were already successfully employed on 2,3-epoxy alcohols or esters.[14] As shown in Table 1, the appropriate choice of Lewis acid allowed to direct, when NR_2 is a tertiary amine, the regioselectivity of the ring opening in C-3 or C-2 position. In fact, using A or B methods the expected 3-azido-2-hydroxy amines **5a**–**f** were obtained, whereas using the method C the only isolated products were the 2-azido-3-hydroxy amines **6a**–**c** and **6e**–**f**.[15]

It is of interest to note that the C-2 ring opening observed using $TMSN_3$/Ti(O-*i*-Pr)$_4$ (method C) was really unexpected, because the same reaction conditions applied on 2,3-epoxy alcohols has been reported to give a high C-3 regioselectivity. Therefore we decided to prepare the 2,3-epoxy amine **4d** with a secondary amine at C-1, to test whether the presence of a proton on the C-1 heteroatom was crucial for the course of the reaction.

Actually, the latter example (entry 8) showed that the presence of the proton seemed to be important to direct the regioselectivity of the nucleophilic attach, since in this case only the C-3 derivative **5d** was detected. Evidently, there where different orientations between the epoxides and the source of nucleophile, namely $TMSN_3$/Ti(O-*i*-Pr)$_4$, depending on whether NR_2 is a tertiary or

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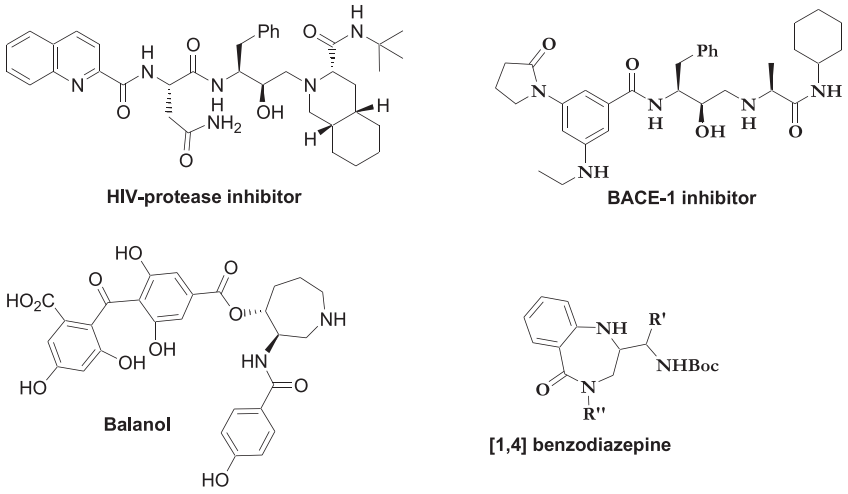
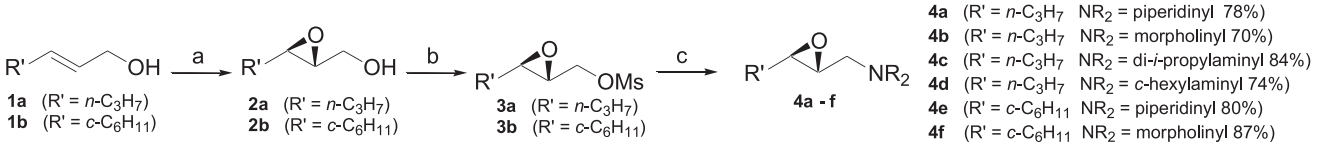
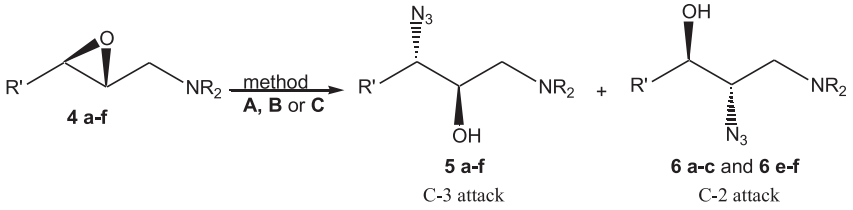


Fig. 1. Examples of molecules containing diaminoalcohol and triamino fragments.



Scheme 1. (a) *m*-CPBA, CH_2Cl_2, rt, 97–98%; (b) CH_3SO_2Cl, Et_3N, DMAP, CH_2Cl_2, rt, 88–95%; (c) R_2NH, neat, 50 °C, 70–87%.

Table 1
Lewis acid-catalyzed azidolysis of 2,3-epoxy amines



Entry	Epoxide	Method[a]	Main product	Yield[b] (%)
1	**4a**	A, B	**5a**	85
2	**4a**	C	**6a**	82
3	**4b**	A, B	**5b**	94
4	**4b**	C	**6b**	84
5	**4c**	A, B	**5c**	87
6	**4c**	C	**6c**	97
7	**4d**	A, B	**5d**	98
8	**4d**	C	**5d**	94
9	**4e**	A, B	**5e**	92
10	**4e**	C	**6e**	96
11	**4f**	A, B	**5f**	86
12	**4f**	C	**6f**	92

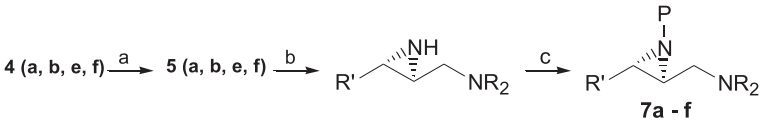
[a] Method A: $TMSN_3$ (1 mmol), $BF_3{\cdot}Et_2O$ (2 mmol), CH_2Cl_2, rt; method B: $TMSN_3$ (1.2 mmol), $ZnCl_2$ (0.04 mmol), neat, 70 °C; method C: $TMSN_3$ (1.04 mmol), Ti(O-*i*-Pr)$_4$ (1.84 mmol), benzene, 90 °C.
[b] The main product was the only product detected (NMR analysis).

secondary amine. In order to rationalize the experimental evidence molecular calculations are currently under investigation.

However, given the interesting results obtained with 2,3-epoxy amines and the key role played by the azide moiety as an amine precursor, we decided to extend our studies on 2,3-aziridine amines, which could give access to triamino sequences. As noted for 2,3-epoxy amines, despite the rich literature on the chemistry of aziridine opening, there are, to the best of our knowledge, only a few reports[16] concerning the ring-opening reactions of 2,3-aziridines amines by the azide group.

The 2,3-epoxy amines were transformed into the corresponding 2,3-aziridine amines through a well known procedure (Scheme 2).[17] Different amines, different substituents R′ on the heterocyclic ring, and different protecting groups of the aziridine nitrogen were used to investigate the influence of steric hindrance and electronic effects on the trends of the reaction.

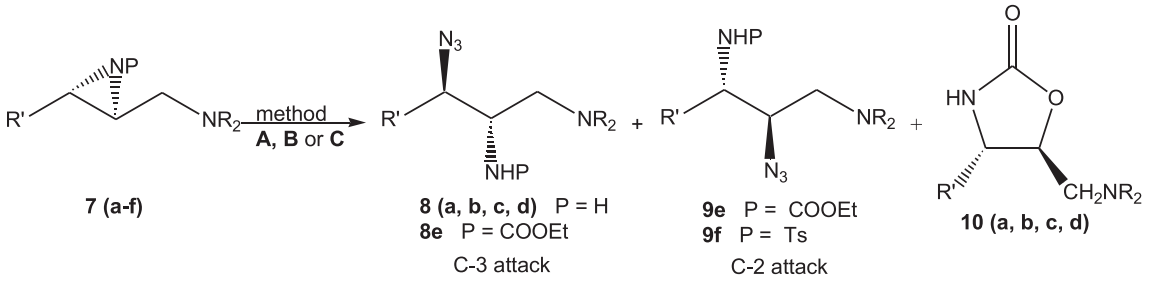
At this point, the same reaction conditions of azidolysis were applied to the N-protected aziridine amines and, as described below, gave different products depending on the reagents used (Table 2).

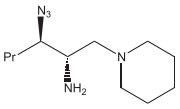
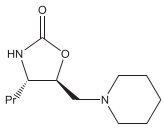
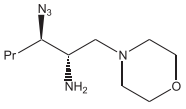
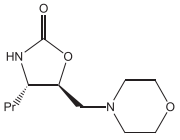
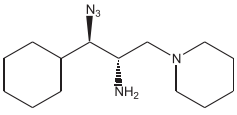
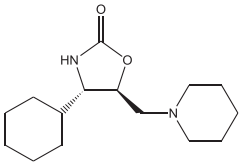
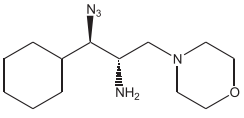
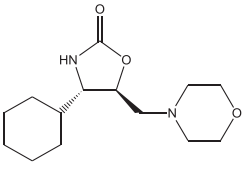


7a R' = *n*-C_3H_7 NR_2 = piperidinyl 78% P = Boc
7b R' = *n*-C_3H_7 NR_2 = morpholinyl 70% P = Boc
7c R' = *c*-C_6H_{11} NR_2 = piperidinyl 78% P = Boc
7d R' = *c*-C_6H_{11} NR_2 = morpholinyl 70% P = Boc
7e R' = *c*-C_6H_{11} NR_2 = piperidinyl 80% P = COOEt
7f R' = *c*-C_6H_{11} NR_2 = piperidinyl 87% P = Ts

Scheme 2. (a) $TMSN_3$, BF_3, rt, 74–98%; (b) Ph_3P, CH_3CN, rt then reflux; (c) (i) for Boc: $(Boc)_2O$, DMAP, CH_2Cl_2, rt, 65–72%; (ii) for CO_2Et: $ClCO_2Et$, Et_3N, Et_2O, 0 °C, 68%; (iii) for Ts: TsCl, pyr, −20 °C, 62%.

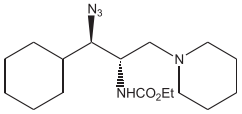
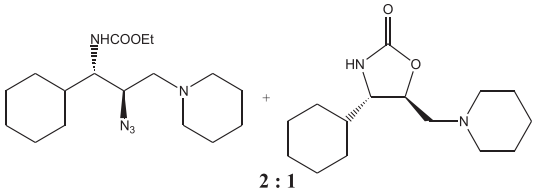
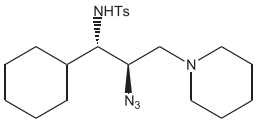
Table 2
Lewis acid-catalyzed azidolysis of 2,3-aziridine amines



Entry	Aziridine	Method[a]		Main product	Yield[b] (%)
1	**7a**	A, B	**8a**		82
2	**7a**	C	**10a**		74
3	**7b**	A, B	**8b**		98
4	**7b**	C	**10b**		74
5	**7c**	A, B	**8c**		86
6	**7c**	C	**10c**		92
7	**7d**	A, B	**8d**		86
8	**7d**	C	**10d**		92

(*continued on next page*)

Table 2 (*continued*)

Entry	Aziridine	Method[a]	Main product	Yield[b] (%)
9	**7e**	A, B	**8e** 	83
10	**7e**	C	**9e**+**10c**  2 : 1	90
11	**7f**	C	**9f** 	92

[a] Method A: $TMSN_3$ (1 mmol), $BF_3{\cdot}Et_2O$ (2 mmol), CH_2Cl_2, rt; method B: $TMSN_3$ (1.2 mmol), $ZnCl_2$ (0.04 mmol), neat, 70 °C; method C: $TMSN_3$ (1.04 mmol), Ti(O-*i*-Pr)$_4$ (1.84 mmol), benzene, 90 °C.

[b] The major regioisomer was the only product detected (NMR analysis).

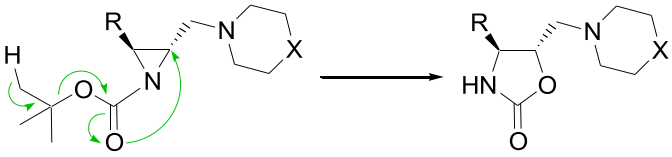
The methodologies A ($TMSN_3/BF_3{\cdot}Et_2O$) and B ($TMSN_3/ZnCl_2$) led to the expected C-3 attack of the heterocyclic ring and gave the 3-azido-2-amine derivatives in satisfactory yield.[18] Note that during the work-up, the 2,3-aziridine amines were converted into the corresponding deprotected derivatives due to the acidic conditions (see Experimental section).[19]

On the other hand, when the 2,3-aziridine amines were protected with the acid stable –COOEt group, the reactions with the methodologies A and B still afforded only the protected 3-azido-2-*N*-(ethoxycarbonyl)-amino derivative (entry 9).

Unexpectedly, the use of $TMSN_3$/Ti(O-*i*-Pr)$_4$ on the 2,3-aziridine *N*-Boc protected amines **7a**–**d** did not afford azide derivatives, but the substrates were quantitatively converted into the corresponding oxazolidin-2-ones. The observed ring expansion proceeded with complete regio- and stereo-selectivity, giving only *trans*-5-aminomethyl-oxazolidin-2-ones (entries 2, 4, 6, 8).

The regiochemistry of the rearrangement was established by spin–spin decoupling experiments. Instead regarding the stereochemistry of the 4,5-disubstituted oxazolidin-2-ones, the coupling constant $J_{4,5}$ values were in all cases in accordance with a trans relationship (5.0–6.0 Hz).[20] To confirm further the trans-stereochemistry of the oxazolidin-2-ones, the molecular structure of the crystalline **10d** was studied by X-ray diffraction. The crystallographic data are consistent with the structure shown in Fig. 2, or the inverted one, both confirming the trans-stereochemistry of the HN–C4–C5–O fragment.

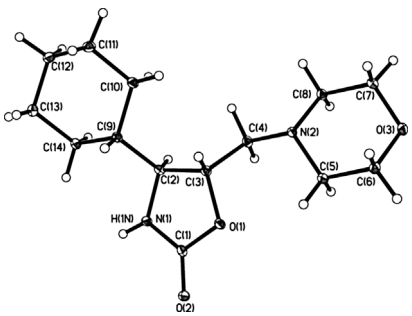
The ring expansion under the reaction conditions C can be rationalized via an intramolecular rearrangement (Scheme 3) where the Lewis acid catalyzes the formation of the incipient tertiary carbocation on $-C(CH_3)_3$ with the elimination of a molecule of isobutene.[21] To justify the overall retention of the stereochemistry, a possible anchimeric assistance of the piperidine/morpholine ring can be invoked.[22]

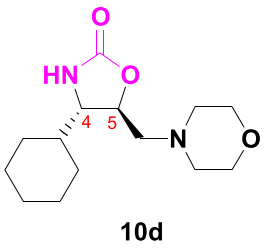


Scheme 3. Rearrangement of *N*-Boc aziridine to oxazolidin-2-one.

The results seemed to suggest that the course of reaction was independent of the presence of $TMSN_3$; in fact the same product was also obtained when the reaction was carried out only with Ti(O-*i*-Pr)$_4$, although in a longer time.

Utilizing the ethyl carbamate as protecting group the reaction led to a mixture of the oxazolidin-2-one and the C-2 opening product in ratio 1:2 (entry 10). Evidently, the lower ability of the ethyl group to form the incipient carbocation compared with the *tert*-butyl one is responsible for the decrease of the ring expansion,





10d

Fig. 2. X-ray structure of the oxazolidin-2-one **10d**.

in favor of the C-2 opening one. When we used the *N*-tosyl aziridine amine **7f** that cannot make oxazolidinone, the reaction gave exclusively the C-2 opening product (entry 11).

In conclusion, we have developed a Lewis acid-mediated regioselective azidolysis of 2,3-three membered heterocyclic amines, using $TMSN_3$ as the source of azide.

The peculiarity of these results is due to the possibility to access to different aminoalcoholic and triaminic fragments (Fig. 3) simply by choosing appropriately the Lewis acid and, in the case of aziridine, the N-functionalization. The products are generally obtained in high chemical yields and often without requiring any purification.

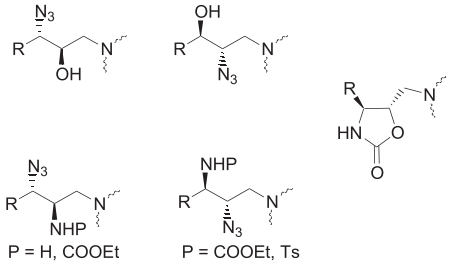


Fig. 3. Aminoalcoholic and triaminic fragments accessible with the presented methodologies.

2. Experimental section

The following compounds **2a** and **2b** are already known.[23]

2.1. General procedure for the 2,3-epoxy amines preparation

To a solution of the appropriate 2,3-epoxy alcohol (1 mmol) in CH_2Cl_2 (1.6 mL), Et_3N (0.27 mL, 2 mmol) and a catalytic amount of DMAP were added. After being stirred at 0 °C, methane sulfonyl chloride (0.08 mL, 1 mmol) was added dropwise. After 2 h (TLC monitoring), the reaction was quenched with ice cold water, the organic layers were extracted with CH_2Cl_2 (20 mL), washed with ice cold HCl 1 N (5 mL), saturated aqueous $NaHCO_3$ (5 mL, saturated aqueous), and then brine (15 mL). Organic extracts were dried (Na_2SO_4) and then evaporated in vacuo. To the crude mesylate was then added the suitable amine (2.5 mmol) and the mixture was stirred at 70 °C for 2 h. After this time the mixture was diluted with EtOAc (10 mL), washed with brine (5×3 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by flash chromatography on silica gel (hexane/EtOAc and/or $CHCl_3$/MeOH).

2.1.1. 1-(3-Propyl-oxiranylmethyl)-piperidine ***4a***. Colorless oil (143 mg, 78% yield); R_f=0.33 (silica gel, EtOAc/hexanes 3:7); IR (neat): 3040, 2970, 1463, 1240, 1090, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.68 (3H, t, J=7.4 Hz, CH_3), 1.05–1.52 (10H, m), 2.04 (1H, dd, J=6.4, 13.2 Hz, CH_aN), 2.07–2.27 (4H, m, $CH_2N_{piperid}$), 2.32 (1H, dd, J=3.9, 13.2 Hz, CH_bN), 2.33–2.41 (1H, m, *CH*O), 2.58 (1H, ddd, J=2.2, 3.9, 6.4 Hz, *CH*O); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.4, 18.8, 23.6, 25.4, 33.3, 54.4, 56.0, 56.1, 60.8. HRMS m/z calcd for $C_{11}H_{21}NO+H^+$: 184.1701; found 184.1698.

2.1.2. 4-(3-Propyl-oxiranylmethyl)-morpholine ***4b***. Colorless oil (130 mg, 70% yield); R_f=0.40 (silica gel, EtOAc/hexanes 1:1); IR (neat): 3060, 2980, 2885, 1485, 1380, 1260, 890 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.87 (3H, t, J=6.9 Hz, CH_3), 1.31–1.52 (4H, m), 2.23 (1H, dd, J=6.8, 13.1 Hz, CH_aN), 2.37–2.57 (4H, m, CH_2N_{morph}), 2.57–2.67 (2H, m, *CH*O+CH_bN), 2.79 (1H, ddd, J=2.3, 3.5, 6.8 Hz, *CH*O), 3.65 (4H, t, J=4.7 Hz, CH_2O_{morph}); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.7, 19.1, 33.6, 53.7, 55.9, 56.2, 60.6, 66.5. HRMS m/z calcd for $C_{10}H_{19}NO_2+H^+$: 186.1494; found 186.1491.

2.1.3. Diisopropyl-(3-propyl-oxiranylmethyl)-amine ***4c***. Colorless oil (167 mg, 84% yield); R_f=0.52 (silica gel, EtOAc/hexanes 2:8); IR (neat): 2960, 2720, 1350, 1230, 1110, 975 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.85 (3H, t, J=7.1 Hz, CH_3), 0.91 (12H, d, J=6.6 Hz, 4CH_3), 1.31–1.48 (4H, m), 2.44 (1H, dd, J=4.8, 14.5 Hz, CH_aN), 2.52 (1H, dd, J=4.3, 14.5 Hz,, CH_bN), 2.55–2.67 (2H, m, *CH*O), 2.95 (2H, sept, J=6.6 Hz, CH_{isopr}); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.7, 19.1, 20.4, 20.7, 33.8, 46.8, 48.7, 57.9, 59.4. HRMS m/z calcd for $C_{12}H_{25}NO+H^+$: 200.2014; found 200.2012.

2.1.4. Cyclohexyl-(3-propyl-oxiranylmethyl)-amine ***4d***. Colorless oil (146 mg, 74% yield); R_f=0.22 (silica gel, EtOAc/hexanes 2:8); IR (neat): 3240, 3070, 2640, 1210, 1030, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.95 (3H, t, J=6.9 Hz, CH_3), 0.97–1.95 (15H, m), 2.38–2.43 (1H, m, $CHNH_{cyclohex}$), 2.63 (1H, dd, J=6.0, 12.5 Hz, CH_aN), 2.75–2.79 (1H, m, *CH*O), 2.80–2.86 (1H, m, *CH*O), 2.95 (1H, dd, J=3.5, 12.5 Hz, CH_bN); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.9, 19.3, 24.6, 25.7, 33.0, 33.1, 33.5, 48.0, 56.2, 56.7, 57.7. HRMS m/z calcd for $C_{12}H_{23}NO+H^+$: 198.1858; found 198.1854.

2.1.5. 1-(3-Cyclohexyl-oxiranylmethyl)-piperidine ***4e***. Colorless oil (178 mg, 80% yield); R_f=0.33 (silica gel, EtOAc/hexanes 3:7); IR (neat): 3061, 3028, 2960, 1320, 1201, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.92–1.91 (17H, m), 2.27 (1H, dd, J=6.3, 13.2 Hz, CH_aN), 2.31–2.48 (5H, m, *CH*O+$CH_2N_{piperid}$), 2.52 (1H, dd, J=4.0, 13.2 Hz, CH_bN), 2.87 (1H, ddd, J=2.3, 4.0, 6.3 Hz, *CH*O); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=23.8, 25.2, 25.3, 25.5, 25.9, 28.6, 29.2, 39.4, 54.5, 55.1, 60.9, 61.1. HRMS m/z calcd for $C_{14}H_{25}NO+H^+$: 224.2014; found 224.2009.

2.1.6. 4-(3-Cyclohexyl-oxiranylmethyl)-morpholine ***4f***. Colorless oil (195 mg, 87% yield); R_f=0.45 (silica gel, EtOAc/hexanes 1:1); IR (neat): 3090, 3015, 2970, 1310, 1195, 1050, 711 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.81–1.35 (6H, m), 1.41–1.92 (5H, m), 2.17 (1H, dd, J=6.6, 13.1 Hz, CH_aN), 2.25–2.43 (5H, m, *CH*O+CH_2N_{morph}), 2.48 (1H, dd, J=3.7, 13.1 Hz, CH_bN), 2.76 (1H, ddd, J=2.3, 3.7, 6.1 Hz, *CH*O), 3.65 (4H, t, J=4.6 Hz, CH_2O_{morph}); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=25.2, 25.3, 25.9, 28.6, 29.2, 39.4, 53.7, 54.7, 60.6, 60.7, 66.5. HRMS m/z calcd for $C_{13}H_{23}NO_2+H^+$: 226.1807; found 226.1804.

2.2. General procedure of the azidolysis

2.2.1. Methodology A. To a stirred solution of the epoxy amine **4** (1 mmol) in dry CH_2Cl_2 (3 mL) were added dropwise, under argon atmosphere, $TMSN_3$ (115 mg, 1 mmol) and $BF_3{\cdot}OEt_2$ (283 mg, 0.25 mL, 2 mmol) and the reaction mixture was left stirring at room temperature. After complete consumption of the substrate (TLC monitoring), the mixture was diluted with CH_2Cl_2 (10 mL), washed with $NaHCO_3$ (3 mL), brine (3×3 mL), dried (Na_2SO_4) and the solvent removed under reduced pressure. Often the crude product was characterized without further purification.

2.2.2. Methodology B. The epoxy amine **4** (1 mmol), $TMSN_3$ (1.2 mmol), and $ZnCl_2$ (0.04 mmol) were stirred at 68 °C for 15 h at which time an additional of zinc chloride (0.04 mmol) was added. After a total reaction time of 45 h, the reaction mixture at 20 °C was treated with THF (0.64 mL), acetic acid (0.064 mL), and HCl concd (0.027 mL) and then stirred for 30 min. The reaction mixture was diluted with EtOAc (10 mL) and $NaHCO_3$ (3 mL) and washed with H_2O (4 mL) and the layers were separated. The aqueous phase was extracted with EtOAc (3×3 mL). The combined organic extracts were washed with brine (3×4 mL), dried (Na_2SO_4), and

concentrated in vacuo. Often the crude product was characterized without further purification.

2.2.3. Methodology C. A solution of Ti(O-*i*-Pr)$_4$ (1.84 mmol) and $TMSN_3$ (1.04 mmol) in benzene (4 mL) was heated at 90 °C for 4 h. To the heating yellow solution was added epoxy amines **4** (1 mmol) in benzene (1 mL) and reflux was continued for 0.8–4 h. The solution was then cooled to 0 °C, H_2SO_4 15% (8.2 mL) was added, and the mixture was stirred vigorously for 1 h. Upon cooling the reaction mixture was diluted with EtOAc (10 mL) and $NaHCO_3$ (3 mL) and washed with H_2O (5×4 mL) and brine (1 mL), and finally dried (Na_2SO_4) before removal of the solvent in vacuo. The resulting product was characterized without further purification.

2.2.4. (3R,2S*)-3-Azido-1-piperidin-1-yl-hexan-2-ol* ***5a***. Pale yellow oil (192 mg, 85% yield); R_f=0.44 (silica gel, $CHCl_3$/MeOH 9:1); IR (neat): 3370, 3020, 2115, 1235, 1021 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.94 (3H, t, J=6.9 Hz, CH_3), 1.24–1.68 (10H, m), 2.23–2.47 (5H, m, CH_2N$_{piperid}$+OH), 2.50–2.68 (2H, m, CH_2N), 3.34–3.48 (1H, m, CHN$_3$), 3.67 (1H, ddd, J=5.12, 5.12, 9.58 Hz, CHOH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): 13.8, 19.6, 24.2, 26.1, 32.5, 54.6, 59.9, 65.5, 68.5; HRMS m/z calcd for $C_{11}H_{22}N_4O$+H^+: 227.1872; found 227.1875.

2.2.5. (2S,3R*)-2-Azido-1-piperidin-1-yl-hexan-3-ol* ***6a***. Pale yellow oil (192 mg, 82% yield); R_f=0.51 (silica gel, $CHCl_3$/MeOH 9:1); IR (neat): 3620, 3020, 2101, 1230, 1141 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.95 (3H, t, J=7.0 Hz, CH_3), 1.30–1.68 (10H, m), 2.24–2.57 (6H, m), 2.63 (1H, br s, OH), 3.53 (1H, ddd, J_1=J_2=5.9, 2.8 Hz, CHN$_3$), 3.64–3.76 (1H, m, CHOH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=14.0, 19.0, 23.8, 25.9, 35.6, 55.4, 60.1, 61.8, 73.0; HRMS m/z calcd for $C_{11}H_{22}N_4O$+H^+: 227.1872; found 227.1877.

2.2.6. (3R,2S*)-3-Azido-1-morpholin-4-yl-hexan-2-ol* ***5b***. Pale yellow oil (214 mg, 94% yield); R_f=0.23 (silica gel, EtOAc/hexanes 3:7); IR (neat): 3520, 3020, 2112, 1265, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.92 (3H, t, J=7.0 Hz, CH_3), 1.20–1.72 (4H, m), 2.34–2.50 (5H, m, CH_2N$_{morph}$+OH), 2.55–2.82 (2H, m, CH_2N), 3.33–3.55 (1H, m, CHN$_3$), 3.58–3.89 (5H, m, CH_2O$_{morph}$+CHOH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.6, 19.5, 32.3, 53.5, 59.8, 65.1, 66.7, 68.4; HRMS m/z calcd for $C_{10}H_{20}N_4O_2$+H^+: 229.1665; found 229.1668.

2.2.7. (2S,3R*)-2-Azido-1-morpholin-4-yl-hexan-3-ol* ***6b***. Pale yellow oil (192 mg, 84% yield); R_f=0.51 (silica gel, EtOAc/hexanes 2:1); IR (neat): 3520, 3025, 2108, 1290, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.93 (3H, t, J=7.0 Hz, CH_3), 1.36–1.64 (4H, m), 2.59 (4H, t, J=4.6 Hz, CH_2N$_{morph}$), 2.68 (2H, d, J=6.0 Hz, CH$_2$N), 3.44–3.60 (2H, m, CHN$_3$+OH), 3.60–3.68 (1H, m, CHOH), 3.70 (4H, t, J=4.5 Hz, CH_2O$_{morph}$); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.9, 18.9, 36.1, 54.2, 60.1, 62.2, 66.8, 72.6; HRMS m/z calcd for $C_{10}H_{20}N_4O_2$+H^+: 229.1665; found 229.1669.

2.2.8. (3R,2S*)-3-Azido-1-diisopropylamino-hexan-2-ol* ***5c***. Pale yellow oil (210 mg, 87% yield); R_f=0.18 (silica gel, EtOAc/hexanes 1.5:8.5); IR (neat): 3420, 3020, 2109, 1215, 1030 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.89 (3H, t, J=6.9 Hz, CH_3), 0.97 (3H, s, CH_3), 0.99 (3H s, CH_3), 1.01 (3H, s, CH_3), 1.03 (3H, s, CH_3), 1.28–1.34 (4H, m), 2.68–2.77 (3H, m, CH_2N+OH), 3.07 (2H, sept, J=6.55 Hz, CH(CH$_3$)$_2$), 3.42 (1H, ddd, J=3.0, 5.3, 8.3 Hz, CHN$_3$), 3.60 (1H, m, CHOH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.8, 18.8, 19.9, 20.7, 36.2, 46.8, 48.3, 64.5, 71.8; HRMS m/z calcd for $C_{12}H_{26}N_4O$+H^+: 243.2185; found 243.2188.

2.2.9. (2S,3R*)-2-Azido-1-diisopropylamino-hexan-3-ol* ***6c***. Pale yellow oil (235 mg, 97% yield); R_f=0.52 (silica gel, EtOAc/hexanes 1.5:8.5); IR (neat): 3560, 3020, 2101, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.80 (3H, t, J=7.0 Hz, CH_3), 0.97 (3H, s, CH_3), 0.99 (3H, s, CH_3), 1.01 (3H, s, CH_3), 1.04 (3H, s, CH_3), 1.43 (4H, m), 2.75 (2H, dd, J_1=J_2=4.4 Hz, CH_2N), 3.07 (2H, sept, J=6.7 Hz, CH(CH$_3$)$_2$), 3.40 (2H, m, CHOH+OH), 3.58 (1H, m, CHN$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.4, 19.5, 32.1, 53.0, 59.1, 64.8, 66.2, 68.0; HRMS m/z calcd for $C_{12}H_{26}N_4O$+H^+: 243.2185; found 243.2188.

2.2.10. (3R,2S*)-3-Azido-1-cyclohexylamino-hexan-2-ol* ***5d***. Pale yellow oil (method. A or B: 235 mg, 98% yield; method. C: 225 mg, 94% yield); R_f=0.49 (silica gel, $CHCl_3$/MeOH 9.2:0.8); IR (neat): 3450, 3022, 2112, 1220, 1020 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.95 (3H, t, J=7.0 Hz, CH_3), 1.01–1.85 (15H, m), 2.31–2.55 (1H, m, CH_{cyclo}), 2.62 (1H, dd, J=8.9, 12.2 Hz, CH_aN), 2.82 (1H, dd, J=3.6, 12.2 Hz, CH_bN), 2.87–3.05 (1H, br s, OH), 3.31–3.45 (1H, m, CHN$_3$), 3.56 (1H, ddd, J=3.6, 5.3, 8.9 Hz, CHOH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.8, 2.0, 24.9, 25.9, 32.6, 33.4, 33.7, 47.4, 56.6, 65.6, 71.3; HRMS m/z calcd for $C_{12}H_{24}N_4O$+H^+: 241.2028; found 241.2031.

2.2.11. (1R,2S*)-1-Azido-1-cyclohexyl-3-piperidin-1-yl-propan-2-ol* ***5e***. Pale yellow oil (245 mg, 92% yield); R_f=0.43 (silica gel, $CHCl_3$/MeOH 9.6:0.4); IR (neat): 3350, 3020, 2115, 1215, 1050 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.99–1.38 (6H, m), 1.40–2.12 (11H, m), 2.24–2.86 (6H, m, CH_2N$_{piperid}$+CH_2N), 3.27 (1H, dd, J_1=J_2=5.9 Hz, CHN$_3$), 3.65 (1H, br s, OH), 3.74–3.94 (1H, m, CHOH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=24.1, 25.8, 25.9, 26.1, 26.2, 28.7, 30.4, 38.9, 54.6, 60.3, 65.7, 71.5; HRMS m/z calcd for $C_{14}H_{26}N_4O$+H^+: 267.2185; found 267.2186.

2.2.12. (1R,2S*)-2-Azido-1-cyclohexyl-3-piperidin-1-yl-propan-1-ol* ***6e***. Pale yellow oil (255 mg, 96% yield); R_f=0.37 (silica gel, EtOAc/hexanes 4:6); IR (neat): 3320, 3010, 2105, 1220 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.84–1.80 (16H, m), 1.96–2.11 (1H, m), 2.30–2.48 (3H, m, CH_2N$_{piperid}$+OH), 2.54–2.63 (2H, m, CH_2N$_{piperid}$), 2.65 (1H, dd, J=5.8, 13.6 Hz, CH_aN), 2.75(1H, dd, J=4.0, 13.6 Hz, CH_bN), 3.55 (1H, dd, J=1.9, 8.2 Hz, CHO), 3.58 (1H, ddd, J=1.9, 4.0, 5.8 Hz, CHN$_3$); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=23.9, 25.9, 26.0, 26.3, 28.9, 29.0, 40.6, 55.6, 60.0, 61.0, 77.5; HRMS m/z calcd for $C_{14}H_{26}N_4O$+H^+: 267.2185; found 267.2188.

2.2.13. (1R,2S*)-1-Azido-1-cyclohexyl-3-morpholin-4-yl-propan-2-ol* ***5f***. Pale yellow oil (230 mg, 86% yield); R_f=0.32 (silica gel, EtOAc/hexanes 1:1); IR (neat): 3520, 3023, 2103, 1285, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.93–1.37 (5H, m), 1.37–1.96 (6H, m), 2.19–2.81 (6H, m, CH_2N$_{morph}$+CH_2N), 3.22 (1H, dd, J_1=J_2=5.7 Hz, CHN$_3$), 3.70 (5H, br t, J=4.9 Hz, CH_2O$_{morph}$+OH), 3.79 (1H, ddd, J=4.7, 5.7, 9.3 Hz, CHOH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=24.6, 26.8, 27.9, 32.6, 54.4, 60.3, 65.4, 68.3, 71.2; HRMS m/z calcd for $C_{13}H_{24}N_4O_2$+H^+: 269.1978; found 269.1982.

2.2.14. (1R,2S*)-2-Azido-1-cyclohexyl-3-morpholin-4-yl-propan-1-ol* ***6f***. Pale yellow oil (192 mg, 92% yield); R_f=0.37 (silica gel, EtOAc/hexanes 4:6); IR (neat): 3620, 3020, 2101, 1245, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.81–1.39 (5H, m), 1.39–2.09 (6H, m), 2.36–2.95 (6H, m, CH_2N$_{morph}$+CH_2N), 3.28 (1H, dd, J=2.2, 8.1 Hz, CHOH), 3.55–3.86 (1H, m, CHN$_3$), 3–67 (5H, br t, J=4.4 Hz, CH_2O-$_{morph}$+OH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=25.7, 25.8, 26.1, 28.7, 29.1, 40.7, 54.2, 59.6, 60.6, 66.7, 77.0; HRMS m/z calcd for $C_{13}H_{24}N_4O_2$+H^+: 269.1978; found 269.1980.

2.3. General procedure for the aziridine ring formation

To a stirred solution of the appropriate azido alcohol **5** (1 mmol) in dry CH_3CN (1 mL), PPh_3 (1.2 mmol, 314 mg) was added under N_2 atmosphere and the flask equipped with a monitoring device for the nitrogen release. After 2 h the reaction mixture was heated to the

reflux temperature and stirred for 12 h or until consumption of the substrate (TLC monitoring). The solvent was then removed under reduced pressure, the crude dissolved in cold diethyl ether, filtered, concentrated and used without any purifications in the subsequent aziridine nitrogen protection with the suitable protecting groups.

2.3.1. General procedure for the Boc protection. Under nitrogen atmosphere, the appropriate aziridine **5** (1 mmol) was dissolved in of dry CH_2Cl_2 (10 mL). The Boc_2O (248 mg, 1.1 mmol) and a catalytic amount of DMAP were then added and the reaction mixture stirred at room temperature for 12 h or until consumption of the substrate (TLC monitoring). The solvent was then evaporated under reduced pressure to leave the crude, which was purified by flash chromatography on silica gel.

2.3.2. (2R,3R*) N-tert-Butoxycarbonyl-2-(piperidin-1-ylmethyl)-3-propyl-aziridine* ***7a***. Pale yellow oil (220 mg, 78% yield from **5a**); R_f=0.45 (silica gel, EtOAc/hexanes 6:4); IR (neat): 3060, 2980, 2110, 1718, 1312, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.93 (3H, t, J=7.3 Hz, CH_3), 1.18–1.32 (2H, m), 1.42 (9H, br s, $C(CH_3)_3$), 1.35–1.68 (8H, m), 2.15 (1H, ddd, J=3.2, 4.9, 5.0 Hz, CHN_{azir}), 2.22 (1H, dd, J=6.0, 12.5 Hz, CH_aN), 2.31 (1H, ddd, J=3.2, 5.0, 6.0 Hz, CHN_{azir}), 2.36–2.55 (4H, m, $CH_2N_{piperid}$), 2.60 (1H, dd, J=5.0, 12.5 Hz, CH_bN). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.6, 20.1, 25.6, 27.7, 27.9, 32.7, 40.8, 42.8, 54.3, 60.0, 80.6, 160.4. HRMS m/z calcd for $C_{16}H_{30}N_2O_2$+H^+: 283.2386; found 283.2383.

2.3.3. (2R,3R*) N-tert-Butoxycarbonyl-2-(morpholin-1-ylmethyl)-3-propyl-aziridine* ***7b***. Pale yellow oil (220 mg, 70% yield from **5b**); R_f=0.40 (silica gel, EtOAc/hexanes 1:1); IR (neat): 2990, 2975, 2210, 1725, 1309, 975 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.87 (3H, t, J=7.2 Hz, CH_3), 1.03–1.26 (2H, m), 1.36 (9H, br s, $C(CH_3)_3$), 1.41–1.75 (2H, m), 2.04–2.18 (1H, m, CHN_{azir}), 2.19–2.31 (1H, m, CHN_{azir}), 2.32–2.71 (6H, m, CH_2N_{morph}+CH_2N), 3.63 (4H, t, J=4.6 Hz, CH_2O_{morph}). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.5, 20.1, 27.7, 32.5, 40.6, 42.4, 53.5, 59.7, 66.6, 80.6, 160.2. HRMS m/z calcd for $C_{15}H_{28}N_2O_3$+H^+: 285.2178; found 285.2175.

2.3.4. (2R,3R*) N-tert-Butoxycarbonyl-2-(piperidin-1-ylmethyl)-3-cyclohexyl-aziridine* ***7c***. Yellow oil (252 mg, 78% yield from **5e**); R_f=0.40 (silica gel, EtOAc/hexanes 1:1); IR (neat): 3100, 3060, 2975, 2205, 1725, 1315, 982 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.98–1.31 (4H, m), 1.42 (9H, br s, $C(CH_3)_3$), 1.48–1.89 (13H, m), 1.92–2.03 (1H, m, CHN_{azir}), 2.07 (1H, dd, J=6.7, 13 Hz, CH_aN), 2.37 (1H, ddd, J=3.7, 7.1, 7.1 Hz, CHN_{azir}), 2.48–2.65 (4H, m, $CH_2N_{piperid}$), 2.78 (1H, dd, J=4.4, 13 Hz, CH_bN). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=24.4, 25.7, 25.8, 26.1, 27.9, 30.7, 39.5, 39.6, 54.5, 59.5, 80.5, 160.5. HRMS m/z calcd for $C_{19}H_{34}N_2O_2$+H^+: 323.2699; found 323.2696.

2.3.5. (2R,3R*) N-tert-Butoxycarbonyl-2-(morpholin-1-ylmethyl)-3-cyclohexyl-aziridine* ***7d***. Yellow oil (227 mg, 70% yield from **5f**); R_f=0.38 (silica gel, EtOAc/hexanes 1:1); IR (neat): 3075, 2980, 2210, 1720, 1310, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.01–1.35 (6H, m), 1.42 (9H, br s, $C(CH_3)_3$), 1.55–1.83 (5H, m), 2.07–2.31 (1H, m, CHN_{azir}), 2.18 (1H, dd, J=8.5, 12.6 Hz, CH_aN), 2.34–2.64 (4H, m, CH_2N_{morph}), 2.71–2.87 (1H, m, CHN_{azir}), 2.73 (1H, dd, J=2.3, 12.6 Hz, CH_bN), 3.73 (4H, t, J=4.6 Hz, CH_2O_{morph}). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=24.9, 25.1, 25.5, 27.3, 29.7, 30.2, 38.7, 38.9, 47.4, 53.1, 58.6, 66.1, 79.8, 159.7. HRMS m/z calcd for $C_{18}H_{32}N_2O_3$+H^+: 325.2491; found 325.2488.

2.3.6. (2R,3R*) N-Ethoxycarbonyl-2-(piperidin-1-ylmethyl)-3-cyclohexyl-aziridine* ***7e***. Under N_2 atmosphere, the aziridine **5e** (1 mmol) was dissolved in of anhydrous diethyl ether (3 mL). The Et_3N (1.2 mmol, 121 mg, 0.2 mL) and ethyl chloroformate (1.2 mmol, 130 mg, 0.1 mL) were then added and the reaction mixture stirred at room temperature for 3 h or until consumption of the substrate (TLC monitoring). The mixture was then filtered through a Celite pad and the solvent evaporated under reduced pressure to leave the crude, which was purified by flash chromatography on silica gel affording **7e** as a light yellow oil (235 mg, 80% yield from **5e**); R_f=0.30 (silica gel, $CHCl_3$/MeOH 9:1); IR (neat): 3060, 2980, 1725, 1310, 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.97–1.12 (5H, m), 1.16 (3H, t, J=7.2 Hz, CH_3), 1.25–1.71 (12H, m), 2.01–2.07 (1H, m, CHN_{azir}), 2.11 (1H, dd, J=6.3, 13.2 Hz, CH_aN), 2.37–2.46 (5H, m, $CH_2N_{piperid}$+CHN_{azir}), 2.72 (1H, dd, J=4.2, 13.2 Hz, CH_bN), 4.04 (2H, q, J=7.2 Hz, OCH_2). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.6, 24.9, 25.2, 25.4, 29.9, 38.7, 40.9, 43.8, 54.1, 61.0, 61.6, 160.9. HRMS m/z calcd for $C_{17}H_{30}N_2O_2$+H^+: 295.2386; found 295.2382.

2.3.7. Synthesis of (2R,3R*) N-tosyl-2-(piperidin-1-ylmethyl)-3-cyclohexyl-aziridine (****7f****).* Under N_2 atmosphere, the aziridine **5e** (1 mmol) was dissolved in dry pyridine (1.5 mL) and TsCl (1.1 mmol, 190 mg) was then added. After being stirred at room temperature for 12 h (TLC monitoring), the reaction was diluted with Et_2O (15 mL) and washed with a saturated solution of $CuSO_4$. The organic layers were washed with brine, dried over Na_2SO_4, and then evaporated in vacuo to leave the crude product that was purified by flash chromatography on silica gel affording **7f** as a light yellow oil (329 mg, 87% yield from **5e**). R_f=0.35 (silica gel, EtOAc/hexanes 40:60); IR (neat): 3040, 2969, 1710, 1655, 1603, 1234, 965 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.74–1.97 (17H, m), 2.40 (3H, s, CH_3), 2.24–2.70 (6H, m, $CH_2N_{piperid}$+CH_aN+CHN_{azir}), 2.78 (1H, ddd, J=4.0, 4.4, 8.2 Hz, CHN_{azir}), 3.04 (1H, dd, J=3.9, 13.0 Hz, CH_bN), 7.27 (2H, d, J=8.4 Hz, CH_{arom}), 7.81 (2H, d, J=8.4 Hz, CH_{arom}). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=21.5, 24.0, 25.3, 25.5, 25.8, 25.9, 30.1, 30.6, 38.9, 47.1, 53.4, 54.7, 57.3, 127.6, 129.1, 129.2, 143.8. HRMS m/z calcd for $C_{21}H_{32}N_2O_2S$+H^+: 377.2263; found 377.2259.

2.3.8. (1S,2R*)-2-Azido-1-piperidin-1-ylmethyl-pentylammina* ***8a***. Light yellow oil (method. A or B: 184 mg, 82% yield); R_f=0.24 (silica gel, $CHCl_3$/MeOH 9.2:0.8, two runs); IR (neat): 3380, 3020, 2115, 1240, 1025, 1009, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.94 (3H, t, J=7.0 Hz, CH_3), 1.31–1.83 (10H, m), 2.34–2.78 (6H, m, $CH_2N_{piperid}$+CH_2N), 3.09 (1H, ddd, J=4.4, 4.4, 9.0 Hz, $CHNH_2$), 3.35–3.45 (1H, m, CHN_3), 3.80 (2H, br s); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.7, 19.4, 23.7, 25.2, 32.8, 50.9, 54.7, 60.4, 66.1. HRMS m/z calcd for $C_{11}H_{23}N_5$+H^+: 226.2032; found 226.2028.

2.3.9. (4R,5R*)-5-Piperidin-1-ylmethyl-4-propyl-oxazolidin-2-one* ***10a***. Light yellow oil (method. C: 167 mg, 74% yield); R_f=0.29 (silica gel, $CHCl_3$/MeOH 9.6:0.4); IR (neat): 3100, 2850, 1720, 1593, 1465, 1332, 1210, 830, 750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.04 (3H, t, J=7.3 Hz, CH_3), 1.26–1.95 (10H, m), 2.48–2.98 (6H, m, $CH_2N_{piperid}$+CH_2N), 3.56–3.74 (1H, m, $CHNH$), 3.48–3.69 (1H, m, CHO), 6.50 (1H, br s, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.6, 18.3, 21.8, 24.9, 36.7, 54.6, 56.3, 61.4, 79.5, 158.9; HRMS m/z calcd for $C_{12}H_{22}N_2O_2$+H^+: 227.1760; found 227.1759.

2.3.10. (1S,2R*)-2-Azido-1-morpholin-4-ylmethyl-pentylamine* ***8b***. Light yellow oil (method. A or B: 222 mg, 98% yield); R_f=0.24 (silica gel, $CHCl_3$/MeOH 9.2:0.8, two runs); IR (neat): 3510, 3030, 2110, 1230, 1120, 980, 870 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.92 (3H, t, J=7.0 Hz, CH_3), 1.09–1.66 (4H, m), 2.12–2.67 (6H, m, CH_2N_{morph}+CH_2N), 2.75–3.15 (3H, m, CHN+NH_2), 3.25–3.46 (1H, m, CHN_3), 3.66 (4H, br t, J=4.3 Hz, CH_2O_{morph}); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.7, 19.5, 32.7, 50.8, 53.9, 60.4, 65.7, 66.8. HRMS m/z calcd for $C_{10}H_{21}N_5O$+H^+: 228.1824; found 228.1821.

2.3.11. (4R,5R*)-5-Morpholin-4-ylmethyl-4-propyl-oxazolidin-2-one* ***10b***. Light yellow oil (method. C: 168 mg, 74% yield); R_f=0.34 (silica gel, $CHCl_3$/MeOH 9.2:0.8); IR (neat): 3100, 2860, 1720, 1590, 1460,

1350, 1200, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.92 (3H, t, J=7.2 Hz, CH_3), 1.26–1.63 (4H, m), 2.19–2.73 (6H, m, CH_2N_{morph}+CH_2N), 3.49 (1H, ddd, J_1=J_2=J_3=6.0 Hz, CHN), 3.65 (4H, t, J=4.6 Hz, CH_2O_{morph}), 4.28 (1H, ddd, J_1=J_2=J_3=6.2 Hz, CHO), 6.76 (1H, br s, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=13.7, 18.6, 37.3, 54.2, 56.2, 61.6, 66.7, 80.6, 159.3. HRMS m/z calcd for $C_{11}H_{20}N_2O_3$+H^+: 229.1552; found 229.1552.

2.3.12. (1S,2R*)-2-Azido-2-cyclohexyl-1-piperidin-1-ylmethyl-ethylamine* ***8c****.* Light yellow oil (method. A or B: 230 mg, 86% yield); R_f=0.20 (silica gel, $CHCl_3$/MeOH 4:1); IR (neat): 3430, 3015, 2109, 1210, 1030, 980, 880 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.18–1.98 (17H, m), 2.08–2.95 (8H, m, $CH_2N_{piperid}$+CH_2N+NH_2), 2.98–3.19 (1H, m, $CHNH_2$), 3.48–3.71 (1H, m, CHN_3). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=25.6, 25.9, 26.5, 30.9, 31.3, 33.7, 48.3, 54.1, 61.1, 67.1. HRMS m/z calcd for $C_{14}H_{27}N_5$+H^+: 266.2345; found 266.22342.

2.3.13. (4R,5R*)-4-Cyclohexyl-5-piperidin-1-ylmethyl-oxazolidin-2-one* ***10c****.* Light yellow oil (method. C: 245 mg, 92% yield); R_f=0.32 (silica gel, EtOAc/hexanes 4:1, two runs); IR (neat): 3095, 2855, 2700, 1720, 1595, 1470, 1345, 1210, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.03–1.94 (17H, m), 2.32–2.51 (4H, m, $CH_2N_{piperid}$), 2.44 (1H, dd, J=4.6, 13.5 Hz, CH_aN), 2.56 (1H, dd, J=6.9, 13.6 Hz, CH_bN), 3.22 (1H, dd, J_1=J_2=5.9 Hz, CHNH), 4.40 (1H, ddd, J=4.7, 5.9, 6.7 Hz, CHO), 7.05 (1H, br s, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=23.9, 25.5, 25.6, 25.7, 26.0, 28.0, 28.4, 41.9, 55.1, 61.0, 62.7, 78.3, 159.6. HRMS m/z calcd for $C_{15}H_{26}N_2O_2$+H^+: 267.2073; found 267.2070.

2.3.14. (1S,2R*)-2-Azido-2-cyclohexyl-1-morpholin-4-ylmethyl-ethylamine* ***8d****.* Light yellow oil (method. A or B: 230 mg, 86% yield); R_f=0.15 (silica gel, EtOAc/hexanes 3:1, two runs); IR (neat): 3440, 3020, 2115, 1225, 1020, 980, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.95–1.32 (5H, m), 1.52–1.93 (6H m), 2.32 (1H, dd, J=6.3, 12.8 Hz, CH_aN), 2.41 (1H, dd, J=5.3, 12.8 Hz, CH_bN), 2.45–2.61 (6H, m, CH_2N_{morph}+NH_2), 3.04 (1H, m, $CHNH_2$), 3.62–3.67 (1H, m, CHN_3), 3.68 (4H, t, J=4.7 Hz, CH_2O_{morph}). ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=25.9, 26.0, 26.5, 28.8, 30.9, 39.8, 48.1, 53.8, 62.8, 66.7, 72.6. HRMS m/z calcd for $C_{13}H_{25}N_5O$+H^+: 268.2137; found 268.2135.

2.3.15. (4R,5R*)-4-Cyclohexyl-5-morpholin-4-ylmethyl-oxazolidin-2-one* ***10d****.* Yellow solid, mp=99.8–101.9 (method. C: 247 mg, 92% yield); R_f=0.39 (silica gel, $CHCl_3$/MeOH 96:4); IR (neat): 3105, 2900, 2710, 1722, 1601, 1460, 1350, 1200, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.03–1.47 (6H, m), 1.53–1.86 (5H, m), 2.36–2.72 (6H, m, CH_2N_{morph}+CH_2N), 3.23 (1H, dd, J_1=J_2=6.5 Hz, CHNH), 3.65 (4H, t, J=4.1 Hz, CH_2O_{morph}), 4.40 (1H, ddd, J=4.1, 5.7, 6.5 Hz, CHO), 7.04 (1H, br s, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=25.5, 25.6, 26.0, 28.1, 28.7, 42.0, 54.2, 60.9, 62.4, 66.7, 78.3, 159.3. HRMS m/z calcd for $C_{14}H_{24}N_2O_3$+H^+: 269.1865; found 269.1862.

2.3.16. (1S,2R*)-2-Azido-2-cyclohexyl-1-piperidin-1-ylmethyl-(N-ethoxycarbonyl)-ethylamine* ***8e****.* Light yellow oil (method. A or B: 280 mg, 83% yield) R_f=0.75 (silica gel, EtOAc/hexanes 4:6); IR (neat): 3060, 2980, 2100, 1730, 1320, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.15 (3H, t, J=7.1 Hz, CH_3), 0.95–1.88 (17H, m), 2.09–2.81 (6H, m, $CH_2N_{piperid}$+CH_2N), 3.38–3.45 (1H, m, CHNH), 3.78 (1H, dd, J=1.3, 8.5 Hz, CHN_3), 4.05 (2H, q, J=7.2 Hz, CH_2O), 4.77 (1H, br d, J=10.2 Hz, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=14.2, 21.6, 24.0, 25.4, 25.4, 25.8, 25.8, 30.4, 32.6, 40.2, 54.8, 54.9, 57.0, 61.6, 158.2. HRMS m/z calcd for $C_{17}H_{31}N_5O_2$+H^+: 338.2556; found 338.2554.

2.3.17. (1S,2R*)-2-Azido-1-cyclohexyl-3-piperidin-1-yl-(N-ethoxycarbonyl)-propylamine* ***9e****.* Light yellow oil (method. C: 280 mg, 60% yield); R_f=0.84 (silica gel, EtOAc/hexanes 4:6); IR (neat): 3060, 2980, 2100, 1735, 1315, 980 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.17 (3H, t, J=7.1 Hz, CH_3), 0.87–1.89 (17H, m), 2.13–2.71 (6H, m, $CH_2N_{piperid}$+CH_2N), 3. 34 (1H, ddd, J=1.3, 8.7, 10.2 Hz, CHNH), 3.78 (1H, ddd, J=1.3, 4.2, 9.1 Hz, CHN_3), 4.04 (2H, q, J=7.2 Hz, CH_2O), 4.77 (1H, br d, J=10.2 Hz, NH); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=14.3, 21.5, 24.0, 25.3, 25.5, 25.8, 25.9, 30.1, 30.6,40.2, 54.8, 54.9, 59.0, 60.8, 61.6, 156.5. HRMS m/z calcd for $C_{17}H_{31}N_5O_2$+H^+: 338.2556; found 338.2554.

2.3.18. (1S,2R*)-2-Azido-1-cyclohexyl-3-piperidin-4-yl-(N-tosyl)-propylamine* ***9f****.* Light yellow oil (method. C: 385 mg, 92% yield); R_f=0.84 (silica gel, EtOAc/hexanes 4:6); IR (neat): 3055, 2970, 2098, 1650, 1603, 1235, 1100, 990, 975 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=0.72–1.89 (17H, m), 2.40 (3H, s, CH_3), 2.42–2.78 (4H, m, $CH_2N_{piperid}$), 3.08–3.15 (1H, m, CHNH), 3.21 (1H, dd, J=5.2, 12.4 Hz, CH_aN), 3.31(1H, dd, J=7.6, 12.4 Hz, CH_bN), 3.57–3.56 (1H, m, CHN_3), 4.65 (1H, br d, J=9.7 Hz, NH), 7.28 (2H, d, J=8.2 Hz, CH_{arom}), 7.71 (2H, d, J=8.2 Hz, CH_{arom}); ^{13}C NMR (75.4 MHz, $CDCl_3$, 25 °C): δ=21.0, 21.7, 24.1, 25.2, 25.3, 25.7, 25.9, 31.1, 31.6, 39.5, 54.7, 58.8, 61.0, 126.7, 130.2, 137.1, 142.1. HRMS m/z calcd for $C_{21}H_{33}N_5O_2S$+H^+: 420.2433; found 420.2430.

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Supplementary data

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