JOC The Journal of Organic Chemistry

Article

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J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.7b03189 • Publication Date (Web): 02 Mar 2018

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Lewis acid-catalyzed diastereoselective synthesis of multisubstituted *N*-acylaziridine-2-carboxamides from 2*H*-azirines *via* Joullié–Ugi three-component reaction

Anikó Angyal[a,b], András Demjén[a,b], Edit Wéber[c], Anita K. Kovács[d], János Wölfling[b], László G. Puskás[a], Iván Kanizsai[a,*]

[a]*AVIDIN Ltd., Alsó kikötő sor 11/D, Szeged, H-6726, Hungary;* [b]*Department of Organic Chemistry, University of Szeged, Dóm tér 8, H-6720, Szeged, Hungary;* [c]*SZTE-MTA Lendület Foldamer Research Group, Institute of Pharmaceutical Analysis, University of Szeged, Somogyi u. 4., Szeged, H-6720, Hungary;* [d]*Department of Medical Chemistry, University of Szeged, Dóm tér 8, Szeged 6720, Hungary*

Tel.: +36-62/202107; fax: +36-62/202108; e-mail: i.kanizsai@avidinbiotech.com

Abstract

A $ZnCl_2$-catalyzed diastereoselective Joullié–Ugi three-component reaction from 2*H*-azirines, isocyanides and carboxylic acids has been established. The protocol allows the preparation of highly and diversely functionalized *N*-acylaziridine-2-carboxamide derivatives in up to 82% isolated yields. Moreover, the applicability of *N*-acylaziridines is demonstrated through a variety of transformations.

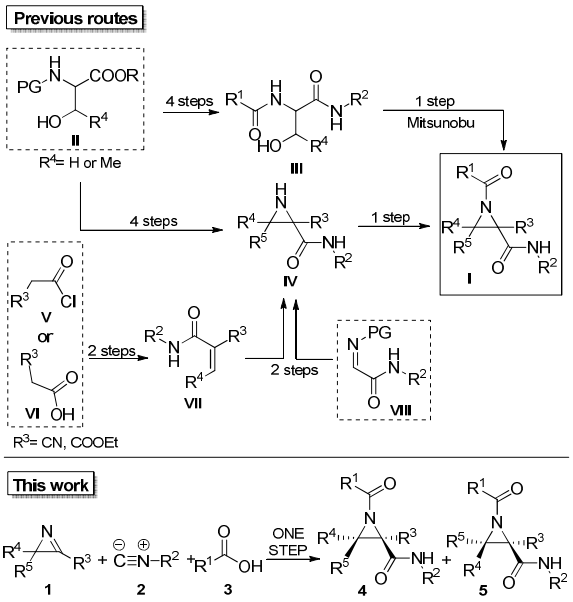
Introduction

Aziridines are not only important building blocks and synthetic intermediates but also present in a variety of biologically active natural (eg. azinomycins and mitomycins) and synthetic compounds exhibiting antibacterial, antimalarial, anticancer and enzyme inhibitory effects.[1]

Due to the structural similarity to α- and β-amino acids, 1*H*-aziridine-2-carboxylic acid (Azy) represents an exceptional interest among aziridines.[2] This useful building block has prompted the preparation of di- and tripeptides by consecutive amino acid couplings towards the NH and carboxyl function of Azy.[3] Following this strategy, a great number of *N*-acylaziridine-2-carboxylates and

-carboxamides were synthesized and tested as cysteine protease inhibitors.[4]

The known synthetic approaches towards *N*-acylaziridine-2-carboxamides **I** are limited and almost exclusively proceed through the formation of aziridine carboxamide intermediate **IV** (Scheme 1). Most of the described methods start from protected amino acids serine and threonine **II** and transform the OH functionality to form the aziridine ring *via* multi-step processes.[5,3b] In addition, a careful choice of protective groups and peptide coupling techniques are required, while the achievable substitution pattern on the aziridine ring is very limited (R^3=H; R^4=H or Me; R^5=H). Alternatively, aziridine-2-carboxamide **IV** can also be obtained from compounds **V** and **VI** containing an active methylene group[6] through Knoevenagel intermediate **VII** or from protected α-iminoglyoxylic derivatives[7] **VIII**. However, these synthetic strategies still suffer from low overall yields and lack of diversity. It is notable, that fully-substituted *N*-acylaziridine-2-carboxamides (R^3, R^4, R^5≠H) have not been reported yet. Therefore, the development of a rapid and straightforward approach to multisubstituted *N*-acylaziridine-2-carboxamides still remains a synthetic challenge.



Scheme 1. Synthetic protocols for *N*-acylaziridine-2-carboxamides.

An efficient opportunity for reducing the number of reaction steps and avoiding protective group strategies is represented by highly-convergent multicomponent reactions (MCRs).[8] The isocyanide-based Ugi four-component reaction is one of the most relevant MCRs, which allows the construction of complex α-aminoacyl amide peptidomimetics in a one-step operation.[9] Although the classical Ugi reaction provides linear products, various

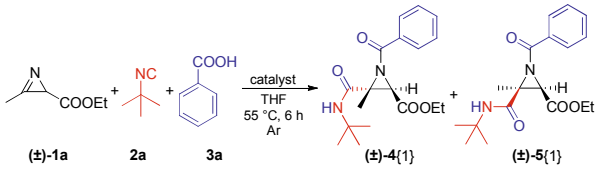
heterocycles (rarely aziridine)[10], can also be accessed either through post-condensation reactions or by the application of bifunctional inputs.[9,11] For example, utilization of cyclic imines in the three-component Joullié–Ugi reaction[12] (JU-3CR) affords diverse five-,[13] six-[13,14] or seven-membered[13,15] *N*-acylated heterocycles.

Here, we describe the first utilization of 2*H*-azirines in the JU-3CR, leading to heavily substituted *N*-acylaziridine-2-carboxamides in a straightforward one-pot procedure.

Results and Discussion

Preliminary investigations were started by examining the reaction of racemic ethyl 3-methyl-2*H*-azirine-2-carboxylate[16a] (**1a**) with *tert*-butyl isocyanide (**2a**) and benzoic acid (**3a**) under the reported Joullié–Ugi 3CR conditions (MeOH, toluene; rt or reflux).[14a,17] However, no conversion was observed. Gratifyingly, performing the model reaction in refluxing THF offered the target product in 8% isolated yield after two days (Table 1, Entry 1). Since Lewis acids could increase the reactivity of azirines,[18] we tested several Lewis- and Brønsted acids as promoters in the model reaction (Table 1, Entries 2–18).

Table 1. Catalyst screen.[a]



(±)-1a 2a 3a (±)-4{1} (±)-5{1}

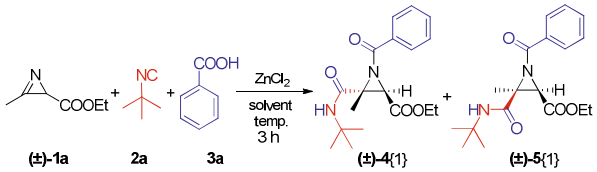
Entry	Catalyst	Yield (%)[b]	dr (*trans*:*cis*)[c]
1[d]	-	8[e]	93:7
2	PTSA	0	-
3	$HClO_4$	0	-
4	$In(OTf)_3$	0	-
5	$Mg(OTf)_2$	0	-
6	$Dy(OTf)_3$	0	-
7	InF_3	0	-
8	$CuBr_2$	0	-
9	$CuCl_2$	0	-
10	$AlCl_3$	0	-
11	$SnCl_2$	12	92:8
12	$FeCl_3$	13	92:8
13	$In(OAc)_3$	16	88:12
14	$Zn(OAc)_2$	20	90:10
15	ZnO	23	87:13
16	$InCl_3$	51	94:6
17	$ZnBr_2$	56	92:8
18	**$ZnCl_2$**	**71**	**93:7**
19	$ZnCl_2$[f]	61	93:7
20	$ZnCl_2$[g]	54	94:6

[a]Reaction conditions: 2*H*-azirine (0.25 mmol), *tert*-butyl isocyanide (1.1 equiv.), benzoic acid (1.1 equiv.), anhydrous THF (0.5 mL), catalyst (25 mol%), argon atmosphere, 55 °C, 6 h. [b]Combined yield of **4**{1} and **5**{1}. Determined by HPLC analysis. [c]The diastereomeric ratio (dr) was determined by HPLC analysis. Both diastereomers were calibrated. [d]48 h, reflux. [e]Isolated yield. [f]10 mol% catalyst was used. [g]50 mol% catalyst was used.

Most of the applied catalysts proved to be ineffective (Table 1, Entries 2–15), except $InCl_3$ and $ZnBr_2$ showing moderate catalytic activity (Table 1, Entries 16 and 17). In contrast, $ZnCl_2$ was found to be a superior catalyst providing the desired *N*-acylaziridines **4**{1} and **5**{1} in 71% combined HPLC yield. Applying both lower (10 mol%) and higher (50 mol%) loadings of $ZnCl_2$ resulted in decreased yields (Table 1, Entries 19 and 20). All reactions gave predominantly *trans*-aziridine **4**{1} with high diastereoselectivity (from 87:13 to 94:6 *trans*:*cis* dr), but the amount of catalyst did not influence the stereochemical outcome. The stereochemistry of *rac*-**4**{1} and *rac*-**5**{1} diastereomers was determined by NOESY experiments (see Supporting Information).

Next, we focused on exploring the effect of solvents, temperature and concentration (Table 2). The reaction was found to tolerate a wide range of media with no distinct changes in the dr (from 89:11 to 93:7; *trans*:*cis*). The developed JU-3CR is mostly favored in non-polar (toluene and 1,4-dioxane) and polar aprotic solvents ($CHCl_3$, THF and MeCN). The only exception is DMF, which was not tolerated (Table 2, Entries 3–8). Of all solvents applied, THF was found to be the best solvent to form aziridine in 72% combined HPLC yield. Additionally, we attempted to accelerate the reaction by using microwave irradiation (Table 2, Entries 9–11). By raising the reaction temperature (80–120 °C) a clear trend of decreased yields and dr was observed. On the other hand, by lowering the concentration of azirine (±)-**1a**, improvements in combined yields and diastereomeric ratios could be achieved (Table 2, Entries 13 and 14).

Table 2. Optimization of the reaction conditions.[a]



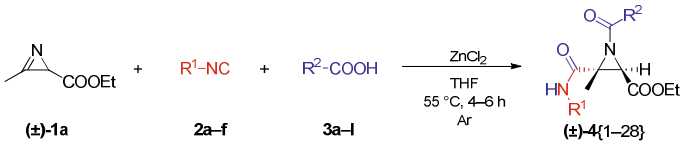
(±)-1a 2a 3a (±)-4{1} (±)-5{1}

Entry	Solvent	Temp. (°C)	Yield (%)[b]	dr[b]
1	EtOH	55	12	91:9
2	IPA	55	40	93:7
3	MeCN	55	56	89:11
4	DMF	55	0	-
5	THF	55	72	93:7
6	$CHCl_3$	55	61	90:10
7	1,4-Dioxane	55	64	92:8
8	Toluene	55	57	91:9
9	THF	80[c]	64	94:6
10	THF	100[c]	58	91:9
11	THF	120[c]	55	88:12
12	THF[d]	55	68	91:9
13	THF[e]	55	77	94:6
14	**THF**[f]	**55**	**81**	**96:4**

[a]Reaction conditions: 2*H*-azirine (0.25 mmol), *tert*-butyl isocyanide (1.1 equiv.), benzoic acid (1.1 equiv.), anhydrous solvent (0.5 mL), anhydrous $ZnCl_2$ (25 mol%), argon atmosphere, 3 h. [b]Combined yield and dr were determined by HPLC analysis. [c]MW conditions: 30 min, 250 W. [d]0.25 mL anhydr. solvent was applied. [e]1 mL anhydr. solvent was applied. [f]2 mL anhydr. solvent was applied and 4 h reaction time was necessary for full conversion.

In further studies, we reacted racemic ethyl 3-methyl-2*H*-azirine-2-carboxylate (**1a**) and *tert*-butyl isocyanide (**2a**) with varied carboxylic acids (**3a–j**) using the optimal reaction conditions (anhydr. $ZnCl_2$, anhydr. THF, argon atmosphere, 55 °C, 4 h) (Table 3, Entries 1–10). Benzoic acids bearing electron donating (3-MeO, 4-OH) or electron-withdrawing (2-Cl) substituents afforded the desired products in moderate to good yields (Table 3, Entries 1–4). Good yields were obtained as well, when phenylacetic acid (**3e**) and 3,4,5-trimethoxycinnamic acid (**3f**) were reacated, providing **4**{5} and **4**{6} in 69% and 60% yields, respectively (Table 3, Entries 5 and 6). Moreover, nicotinic acid, a heteroaromatic carboxylic-acid, could also be subjected to the reaction (Table 3, Entry 7). Gratifyingly, the reaction also tolerated aliphatic carboxylic acids such as acetic and chloroacetic acids giving good yields (Table 3, Entries 8 and 9). To our delight, utilization of the weakly nucleophilic trifluoroacetic acid smoothly afforded the desired *N*-acylaziridine **4**{10} in 54% isolated yield, which demonstrates the robustness of the carboxylic acid scope.

Table 3. Scope of isocyanides and carboxylic acids.[a]



(±)-1a 2a–f 3a–l (±)-4{1–28}

Entry	2 (R^1)	3 (R^2)	4	Yield (%)[b]	dr[c]
1	**2a** R^1=*t*-Bu	**3a** R^2= Ph	**4**{1}	69 (78)	96:4
2	**2a** R^1= *t*-Bu	**3b** R^2= 3-$MeOC_6H_4$	**4**{2}	72 (79)	95:5
3	**2a** R^1= *t*-Bu	**3c** R^2= 4-HOC_6H_4	**4**{3}	56 (62)	93:7
4	**2a** R^1= *t*-Bu	**3d** R^2= 2-ClC_6H_4	**4**{4}	61 (74)	94:6
5	**2a** R^1= *t*-Bu	**3e** R^2= Bn	**4**{5}	69 (75)	94:6
6	**2a** R^1= *t*-Bu	**3f** R^2=3,4,5-$MeOC_6H_2CHCH$	4{6}	60 (69)	95:5
7	**2a** R^1= *t*-Bu	**3g** R^2= 3-pyridyl	**4**{7}	28 (38)	>99
8	**2a** R^1= *t*-Bu	**3h** R^2= Me	**4**{8}	75 (79)	95:5
9	**2a** R^1= *t*-Bu	**3i** R^2= $ClCH_2$	**4**{9}	55 (60)	94:6
10	**2a** R^1= *t*-Bu	**3j** R^2= CF_3	**4**{10}	54 (58)	97:3
11	**2b** R^1= *t*-Octyl	**3a** R^2= Ph	**4**{11}	78 (82)	94:6
12	**2c** R^1= *c*-Hex	**3a** R^2= Ph	**4**{12}	71 (75)	93:7
13	**2d** R^1= Bn	**3a** R^2= Ph	**4**{13}	58 (60)	94:6
14	**2e** R^1= 3,4,5-$MeOC_6H_2$	**3a** R^2= Ph	**4**{14}	38 (40)	97:3
15	**2f** R^1=4-$NO_2C_6H_4$	**3a** R^2= Ph	**4**{15}	60 (69)	97:3
16	**2b** R^1= *t*-Octyl	**3e** R^2= Bn	**4**{16}	77 (80)	95:5
17	**2g** R^1= *n*-Pentyl	**3e** R^2= Bn	**4**{17}	79 (82)	95:5
18	**2c** R^1= *c*-Hex	**3b** R^2= Me	**4**{18}	68 (76)	96:4
19	**2c** R^1= *c*-Hex	**3e** R^2= Bn	**4**{19}	60 (71)	93:7
20	**2c** R^1= *c*-Hex	**3k** R^2= 2,4,6-Me C_6H_2	**4**{20}	80 (85)	96:4
21	**2c** R^1= *c*-Hex	**3l** R^2= 3-FC_6H_4	**4**{21}	77 (86)	93:7
22	**2d** R^1= Bn	**3e** R^2= Bn	**4**{22}	67 (69)	93:7
23	**2d** R^1= Bn	**3f** R^2=3-$MeOC_6H_4$	**4**{23}	58 (60)	96:4
24	**2e** R^1= 3,4,5-$MeOC_6H_2$	**3b** R^2= Me	**4**{24}	22 (34)	99:1
25	**2e** R^1= 3,4,5-$MeOC_6H_2$	**3e** R^2=Bn	**4**{25}	36 (40)	97:3
26	**2e** R^1= 3,4,5-$MeOC_6H_2$	**3a** R^2= 4-$CF_3C_6H_4$	**4**{26}	29 (36)	97:3
27	**2f** R^1= 4-$NO_2C_6H_4$	**3c** R^2= $ClCH_2$	**4**{27}	56 (62)	96:4
28	**2f** R^1= 4-$NO_2C_6H_4$	**3l** R^2= 3-FC_6H_4	**4**{28}	28 (38)	96:4

[a]Reaction conditions: 2*H*-azirine (0.5 mmol), anhydrous THF (4 mL) isocyanide (1.1 equiv.), carboxylic acid (1.1 equiv.), anhydrous $ZnCl_2$ (25 mol%), argon atmosphere, 55 °C, 4 h. [b]Isolated yield of the major *trans* diastereomer (NMR yield in parenthesis). NMR yield was determined by ^{1}H-NMR with 1,3,5-trimethoxybenzene as internal standard. [c]*trans/cis* diastereomeric ratio (determined from crude reaction mixture by LC-MS)

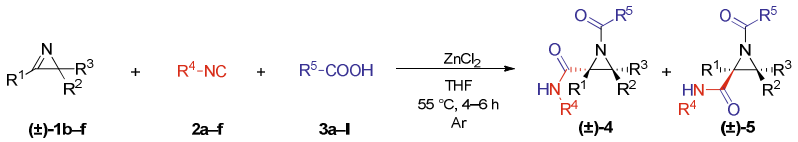
Then, the scope of the reaction with respect to the isocyanide reagent was investigated using (±)-**1a** and **3a** as coupling partners (Table 3, Entries 11–15). When aliphatic isocyanides **2b** and **2c** were applied, the reactions also proceeded smoothly leading to **4**{11} and **4**{12} in 78% and 71% yields. When benzylic **2d** and aromatic isocyanides **2e** and **2f** were subjected to the reaction, lower yields were observed (Table 3, Entries 13–15, 38–60% yields). Interestingly, aromatic isocyanide **2f** bearing the electron-withdrawing nitro group provided a better isolated yield (60%, Entry 15), than the more nucleophilic 3,4,5-trimethoxyphenyl isocyanide **2e** (38%, Entry 14).

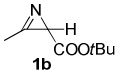
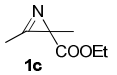
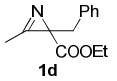
To evaluate the general performance of our method, we carried out further tests with other combinations of the isocyanide and carboxylic acid components (Table 3, Entries 16–28). The protocol allowed the use of a wide range of functional groups and furnished the corresponding *N*-acylaziridines **4** in up to 80% yields with high

diastereoselectivities (ranging from 93:7 to >99:1 *trans*:*cis* dr). As expected, only the isocyanide component affected the outcome of reactions. With benzyl and aliphatic isocyanides (Table 3, Entries 16–23) better isolated yields could be obtained in contrast to aromatic isocyanides (Table 3, Entries 24–28).

To extend the applicability of the reaction, various 2*H*-azirines[16] **1b–f** were utilized under the optimized conditions (Table 4). For comparison, 2*H*-azirines **1b–f** were reacted with *tert*-butyl isocyanide (**2a**) and benzoic acid (**3a**). As expected, azirine **1b** gave the desired *N*-acylaziridines **4**{29–32} with high diastereomeric ratios, albeit in slightly lower yields compared to azirine **1a** (Table 4, Entries 1–4). On the other hand, when fully-substituted 2*H*-azirine **1c** was subjected to the reaction, significant decreases in diastereomeric ratios (58:42 to 64:36) were observed with the concomittant increase in reaction time (6 h) (Table 4, Entries 5–7). These phenemona are most probably due to steric repulsion between the corresponding isocyanide and the R^3 (methyl) substituent of azirine (Table 4, Entries 5–7). Products derived from *tert*-butyl and benzyl isocyanide were isolated as diastereomeric mixtures in 55% and 41% combined yields, while aziridine **4**{34} could be obtained as a pure diastereoisomer. Surprisingly, introducing the sterically more demanding benzyl function at the C2 of azirine (substrate **1d**) resulted in the inversion of stereochemical outcome of the reaction (42:58 dr) and provided *cis* aziridine **5**{36} as major product (Table 4, Entry 8). We were pleased to find that phenyl-substituted 2*H*-azirines **1e** and **1f** were also compatible with the developed JU-3CR method and furnished the corresponding *trans N*-acylaziridines **4**{37–44} with excellent diastereoselectivities (>99%, Table 4, Entries 9–16).

Table 4. Scope of 2*H*-azirines.[a]

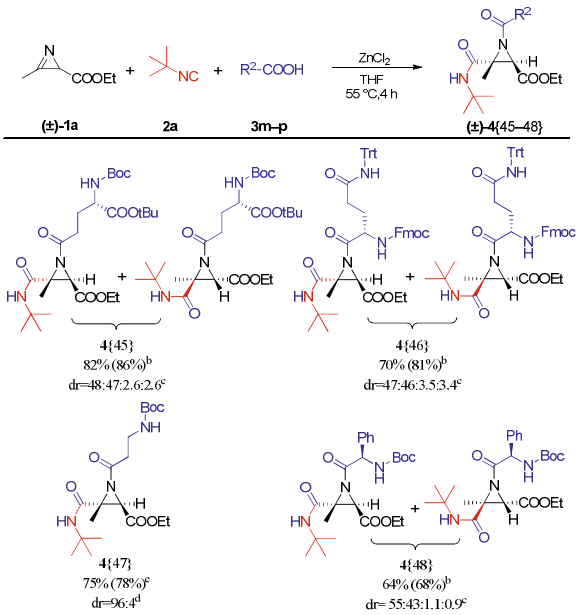


Entry	1	2 (R^4)	3 (R^5)	Isolated product(s)	Isolated yield(%)[c]	NMR yield(%)[d]	dr[e]
1		**2a** R^4= *t*-Bu	**3a** R^5=Ph	**4**{29}	61	74	94:6
2		**2c** R^4= *c*-Hex	**3b** R^5= Me	**4**{30}	54	60	96:4
3	**1b**	**2d** R^4= Bn	**3e** R^5= Ph	**4**{31}	22	23	94:6
4		**2e** R^4= 3,4,5-MeOC_6H_2	**3k** R^5= 2,4,6-Me C_6H_2	**4**{32}	20	35	97:3
5[b]		**2a** R^4= *t*-Bu	**3a** R^5= Ph	**4**{33}+**5**{33}[f]	55[h]	39/21[j]	63:37
6[b]	**1c**	**2c** R^4= *c*-Hex	**3a** R^5= Ph	**4**{34}	31	38/25[j]	63:37
7[b]		**2d** R^4= Bn	**3f** R^5= 3-MeOC_6H_4	**4**{35}+**5**{35}[f]	41[h]	27/19[j]	60:40
8[b]	 **1d**	**2a** R^4= *t*-Bu	**3a** R^5= Ph	**4**{36}, **5**{36}[g]	17/23[i]	22/29[j]	42:58
9		**2a** R^4= *t*-Bu	**3a** R^5= Ph	**4**{37}	70	77	>99
10		**2a** R^4= *t*-Bu	**3b** R^5= Me	**4**{38}	61	64	>99
11	**1e**	**2c** R^4= *c*-Hex	**3k** R^5=2,4,6-Me C_6H_2	**4**{39}	28	33	>99
12		**2e** R^4= 3,4,5-MeOC_6H_2	**3e** R^5= Bn	**4**{40}	43	45	>99
13		**2a** R^4= *t*-Bu	**3a** R^5= Ph	**4**{41}	67	71	>99
14		**2a** R^4= *t*-Bu	**3b** R^5= Me	**4**{42}	62	70	>99
15	**1f**	**2c** R^4= *c*-Hex	**3k** R^5= 2,4,6-Me C_6H_2	**4**{43}	40	44	>99
16		**2e** R^4= 3,4,5-MeOC_6H_2	**3e** R^5= Bn	**4**{44}	51	53	99:1

[a]Reaction conditions: 2*H*-azirine (0.5 mmol), anhydrous THF (4 mL), isocyanide (1.1 equiv.), carboxylic acid (1.1 equiv.), anhydrous $ZnCl_2$ (25 mol%), argon atmosphere, 55 °C, 4 h. [b]6 h reaction time was necessary. [c]Isolated yield of the major *trans* diastereomer. [d]NMR yield was determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [e]*trans*/*cis* diastereomeric ratio (determined from crude reaction mixture by LC-MS). [f]Diastereomeric mixture was isolated. [g]Each diastereomer was isolated. [h]Combined isolated yield. [i]Yields of the separately isolated *trans*/*cis* diastereomers. [j]*trans*/*cis* diastereomers.

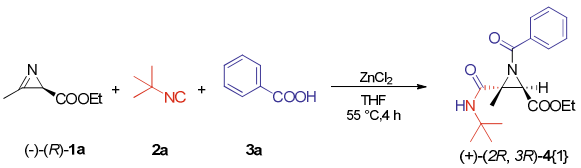
In order to evaluate the suitability of the developed JU-3CR for the construction of aziridine peptidomimetics, we reacted *N*-protected amino acids (L-glutamic acid, L-glutamine, β-alanine and D-phenylglycine derivatives) with *rac*-**1a** and **2a** under the optimized conditions. We were pleased to find that the reaction proceeded well and gave peptides **4**{45–48} in 64–82% isolated yields with high diastereoselectivities (*trans*:*cis* dr) (Table 5).

Table 5. Utilization of *N*-protected aminio acids.[a]



[a]Reaction conditions: 2*H*-azirine (0.5 mmol), anhydrous THF (4 mL), isocyanide (1.1 equiv.), amino acid (1.1 equiv.) anhydrous $ZnCl_2$ (25 mol%), argon atmosphere, 55 °C, 4 h. [b]Combined isolated yield of the two *trans* diastereomers (NMR yield in parenthesis). NMR yield was determined by ^{1}H NMR with 1,3,5-trimethoxybenzene as internal standard. [c]Diastereomeric ratio (*trans*:*trans*:*cis*:*cis*), determined from the crude reaction mixture by LC-MS, [d]Diastereomeric ratio (*trans*:*cis*), [e]Isolated yield of *trans* diastereomer (NMR yield in parenthesis).

Moreover, we investigated the reaction with optically active 2*H*-azirine carboxylic ester (-)-(*R*)-**1a** (Scheme 2.).[16d] Compound (+)-(2*R*,3*R*)-**4**{1} was formed smoothly with no loss of chirality (72% ee). In addition, recrystallization from diethyl ether led to 92% enantiomeric excess (determined by chiral column chromatography).



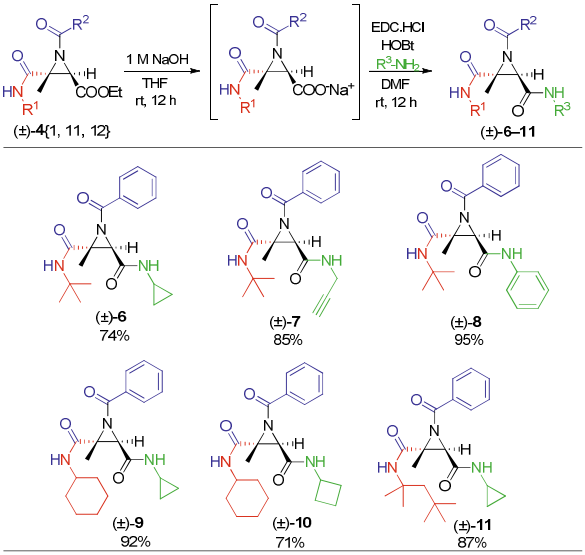
[a]After chromatography.
[b]After chromatography followed by recrystallization from diethyl ether.

Scheme 2. Reaction with optically active 2*H*-azirine.

Transformations of the *N*-acylaziridine products

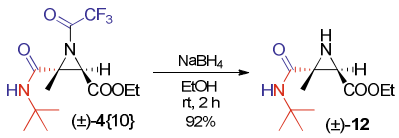
To demonstrate the utility of the JU-3CR products, other transformations were also performed. First, aziridine esters **4**{1}, **4**{11} and **4**{12} were subjected to alkaline hydrolysis followed by EDC/HOBt-mediated amide coupling to give *N*-acylaziridine-2,3-dicarboxamides **6**–**11** (Table 6). To our delight, the multisubstituted aziridine ring withstood the conditions of hydrolysis and coupling reaction affording the corresponding dicarboxamides **6**–**11** in 71–95% isolated yields.

Table 6. Synthesis of *N*-acylaziridine-2,3-dicarboxamides.[a]



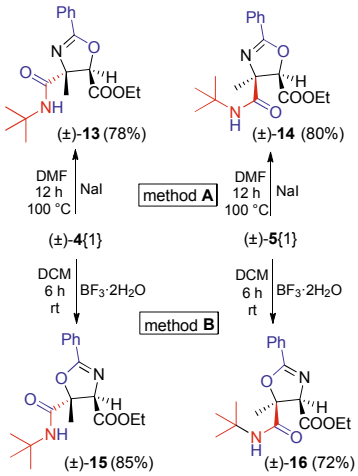
[a]Reaction conditions for hydrolysis: *rac*-*N*-acylaziridine (0.5 mmol), THF (0.65 mL), *aq*. NaOH (1.16 equiv.; 1 M solution), rt, 12 h. Reaction conditions for coupling: DMF (5 mL), EDC hydrochloride (1.16 equiv.), amine (1.0 equiv.) and HOBt (1.38 equiv.), rt, 12 h.

Furthermore, *N*-unsubstituted aziridine (±)-**4**{10} could also be obtained by deprotecting the *N*-trifluoroacetylated derivative (Scheme 3). Treatment with sodium borohydride in EtOH led to compound (±)-**12** in a yield of 92% under mild conditions. According to our knowledge, this is the first example for the removal of a trifluoroacetyl group from aziridine with $NaBH_4$.



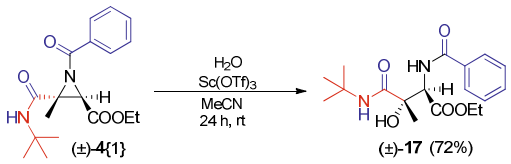
Scheme 3. Synthesis of *N*-unsubstituted aziridine derivative **12**.

Finally, ring-opening and ring-expansion reactions of the JU-3CR products were investigated. Since *N*-acylaziridine-2-carboxamides can be regarded as functionalized α/β -amino acids, their ring opening reactions with water result in highly desirable α-hydroxy-β-amino or β-hydroxy- α-amino acids (mostly catalysed by Lewis acids,[19] eg. $BF_3 \cdot 2H_2O$).[20] On the other hand, *N*-acylaziridines can rearrange into oxazolines, promoted under thermal, acidic or nucleophilic (eg. NaI) conditions.[21] It is notable that the stereo- and regio-chemical outcomes of these reactions greatly depend on both the substitution pattern of the aziridine ring and reaction conditions. The ring expansion of (±)-**4**{1} and (±)-**5**{1} smoothly occured in the presence of NaI in DMF with retention of configuration, and afforded the corresponding *trans*-**13** and *cis*-**14** oxazolines stereoselectively[22] (Scheme 4, Method **A**, 78% and 80% isolated yields). Unexpectedly, three equivalents of $BF_3 \cdot 2H_2O$ in DCM also enabled access to oxazolines, though with inversed regioselectivity (and with the retention of configuration)[22] (Scheme 4, Method **B**, 85% and 72% isolated yields). These observations clearly show that the nucleophilic attack can occur regioselectively at both C2 and C3 depending on reaction conditions (**A** or **B** methods).



Scheme 4. Ring expansion to oxazolines **13**–**16**.

The ring opening of *N*-acylaziridine **4**{1} with water was successfully accomplished in the presence of $Sc(OTf)_3$ catalyst (Scheme 5). The nucleophilic attack occured regioselectively at the C3 position, and afforded β-hydroxy-α-amino acid **17** in a yield of 72% (Scheme 5). Since the mechanism of the ring opening involves an electron-deficient tertiary carbon atom (C3), and requires Lewis acid catalysis, both inversion (S_N2) and retention (Lewis acid-mediated S_N1 mechanism)[23] of C3 configuration could be assumed. In order to determine the stereochemical outcome of the ring opening reaction, however, needs further analytical investigation of product **17**.



Scheme 5. Ring opening reaction with water.

Conclusion

We established a straightforward, one-pot, diastereoselective procedure for the preparation of *N*-acylaziridine-2-carboxamide derivatives through a newly-developed Jullié–Ugi three-component reaction between 2*H*-azirines, isocyanides and carboxylic acids. This robust method tolerates both electron-rich and electron-deficient substrates in all combinations, affording the target multisubstituted aziridines in high diversity with good yields . This MCR procedure also enables the synthesis of short aziridine-based peptidomimetics by coupling *N*-protected amino acids as the carboxylic acid component in a one-step operation. Moreover, the JU-3CR products were converted to *N*-unsubstituted aziridine and dicarboxamide derivatives. In addition, their regioselective transformation to oxazolines and the synthesis of a β-hydroxy-α-amino acid derivative were also accomplished.

Experimental Section

General information: All NMR spectra were recorded at 298 K on a Bruker Avance 500 spectrometer in $CDCl_3$-d_1 or DMSO-d_6. Chemical shifts are reported in δ (ppm) relative to the internal standard (TMS) or the residual solvent signal. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet, dt = doublet of triplet etc.), coupling constants (Hz), and integration. High-resolution mass spectra (HRMS) were measured on a Thermo Scientific Q Exactive hybrid quadrupole-Orbitrap mass spectrometer using HESI ion source. Samples (5 µL from 1 µg/ml solution) were injected to the MS using flow injection method (200 µL/min, water: MeCN 1:1, 0.1% TFA). Melting points (mp) were recorded with an Opti Melt Automated Melting Point System (SRS, Stanford research system). Optical rotation was measured on an Optical Activity AA-55 polarimeter (Optical Activity Ltd.). HPLC-MS analyses were performed on an Agilent 1200 Series equipment with a Waters SQ or Agilent G1946D MS

detector (ESI, operated in positive mode) with Luna C18(2) column (100 Å, 10 µm, 250 x 4.6 mm, Phenomenex) or Kinetex C18 column (100 Å, 5 µm, 250 x 4.6 mm, Phenomenex). The enantiomeric excess was determined by chiral HPLC analysis on a Shimadzu LC-10 VP series equipment with Phenomenex Lux Cellulose-1 column (5µm, 150 x 4.6 mm). Column chromatographies were performed on silica gel (60 Å, 0.063–0.200 mm) from Merck. TLC was performed on fluorescent-indicating plates (aluminum sheets precoated with silica gel 60_{F254}, 1.05554, Merck), and visualization was achieved by UV light (254 nm). Microwave-assisted experiments were conducted using a CEM Discover System in closed vessels under magnetic stirring (temperature was monitored by the built-in external surface sensor). Aromatic isocyanides (4-nitrophenyl isocyanide and 3,4,5-trimethoxyphenyl isocyanide) were prepared according to a known procedure.[24] Racemic 2*H*-azirines[16] **1a**, **1b**, **1e**, **1f** and optically active 2*H*-azirine[16d] (*R*)-**1a** were synthesized according to literature procedures. All other reagents and solvents were commercially available and used without further purification.

Modified procedure and characterization data for racemic 2*H*-azirines 1c and 1d:

(±)-Ethyl 2,3-dimethyl-2*H*-azirine-2-carboxylate (1c) [16a-e]: To a solution of $NH_2OH{\cdot}HCl$ (14.9 mmol, 1.1 equiv.) and NaOH (14.9 mmol, 1.1 equiv.) in 20 mL MeOH ethyl 2-methyl-3-oxobutanoate was added dropwise (13.5 mmol, 1.0 equiv.) at room temperature. After stirring for 2 h, the solvent was removed under reduced pressure. Then 10 mL water was added to the residue, and extracted three times with EtOAc (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to give ethyl 3-(hydroxyimino)-2-methylbutanoate, which was used for the next step without purification.

The crude ketoxime was dissolved immediately in DCM (30 mL) then pyridine (13.5 mmol, 1.0 equiv.) and *p*-toluenesulfonyl chloride (14.9 mmol, 1.1 equiv.) in DCM (20 mL) were added at 0 °C. Then the reaction mixture was stirred for 6 h at 25 °C and after completion of the reaction the solvent was removed in vacuo. Then water (20 mL) was added, and extracted two times with $CHCl_3$ (2 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude material was purified by flash chromatography to yield ethyl 2-methyl-3-((tosyloxy)imino)butanoate (2.8 g, 67%).

To a stirred solution of ketoximetosylate (2.8 g, 8.9 mmol) in 20 mL DCM, triethylamine (9.8 mmol, 1.1 equiv.) was added dropwise at 0 °C. After stirring at 0 °C for 30 min, the mixture was warmed to room temperature and the stirring was continued for 6 h. After the reaction was completed, dilute aqueous HCl (60 mL, 0.05 M) was added and extracted twice with DCM (50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Finally the crude product was purified by vacuum distillation to afford the desired 2*H*-azirine product (904 mg, 72%) as colorless oil. Silica gel TLC R_f = 0.64 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 4.05 (qq, J = 6.9, 3.8 Hz, 2H), 2.47 (s, 3H), 1.33 (s, 3H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO) δ 173.3, 164.3, 61.1, 33.5, 17.8, 14.6, 11.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_7H_{12}NO_2$ 142.0868; Found 142.0863.

(±)-Ethyl 2-benzyl-3-methyl-2*H*-azirine-2-carboxylate (1d): Ethyl 2-benzyl-3-oxo-butyrate was prepared according to the literature.[25]

Ethyl 2-benzyl-3-oxo-butyrate (7.7 mmol, 1.0 equiv) was gradually added to a solution of $NH_2OH{\cdot}HCl$ (7.7 mmol, 1.0 equiv) in pyridine (7 mL) at 0 °C. The solution was stirred for 4 h at 25 °C. Then *p*-toluenesulfonyl chloride (16.9 mmol, 2.2 equiv) was added to the reaction mixture at 0 °C followed by stirring for 12 h at room temperature. After the reaction was completed, aqueous HCl (40 mL, 1 M) was added, and extracted with DCM (2 x 30 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography using hexane/ethyl acetate: 10/1 to afford ethyl 2-benzyl-3-((tosyloxy)imino)butanoate (1.27 g, 84%) as colorless oil. Silica gel TLC R_f = 0.58 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) two isomers (60:40): δ 7.67 (t, J = 8.7 Hz, 4H), 7.43 (t, J = 9.2 Hz, 4H), 7.26 – 7.16 (m, 4H), 7.16 – 7.12 (m, 2H), 7.10 (d, J = 6.8 Hz, 2H), 7.05 (d, J = 6.4 Hz, 2H), 4.21 (t, J = 8.2 Hz, 1H), 4.10 – 3.93 (m, 4H), 3.71 (t, J = 8.1 Hz, 1H), 3.16 (dd, J = 13.9, 6.6 Hz, 1H), 3.04 (dd, J = 14.2, 7.3 Hz, 1H), 2.94 – 2.83 (m, 2H), 2.40 (s, 6H), 1.90 (s, 3H), 1.72 (s, 3H), 1.09 (t, J = 7.1 Hz, 3H), 1.02 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.3, 168.7, 165.1, 163.9, 145.3, 145.2, 137.4, 137.2, 131.9, 131.9, 130.0, 129.9, 128.7, 128.6, 128.4, 128.2, 128.2, 126.7, 126.4, 61.2, 61.1, 52.0, 47.3, 33.7, 33.3, 21.2, 18.4, 14.3, 13.8, 13.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{24}NO_5S$ 390.1375; Found 390.1372.

To a solution of ethyl 2-benzyl-3-((tosyloxy)imino)butanoate (3.3 mmol) in anhydrous THF (8 mL) was added dropwise a solution of DBU (5 mmol, 1.5 equiv.) in anhydrous THF (3.5 mL) at 0 °C. The reaction mixture was allowed to warm up to room

temperature and then stirred until full conversion monitored by TLC (1 h). Then, the solvent was removed under reduced pressure and the residue was purified by column chromatography (hexane/EtOAc : 6/1, silica gel) to give ethyl 2-benzyl-3-methyl-2*H*-azirine-2-carboxylate (558 mg, 78%) as colorless oil. Silica gel TLC R_f = 0.70 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.25 (t, *J* = 7.4 Hz, 2H), 7.17 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 6.8 Hz, 2H), 4.02 (qq, *J* = 7.0, 3.7 Hz, 2H), 3.25 (d, *J* = 14.9 Hz, 1H), 3.01 (d, *J* = 14.9 Hz, 1H), 2.30 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.7, 163.5, 137.9, 129.9, 128.7, 126.7, 61.3, 38.1, 36.8, 14.5, 12.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{16}NO_2$ 218.1181; Found 218.1176.

General procedure and characterization data for *N*-acylaziridine products 4 and 5: To a solution of 2*H*-azirine (0.5 mmol) in anhydrous THF (4 mL), the corresponding isocyanide (1.1 equiv), carboxylic acid (1.1 equiv) and anhydrous $ZnCl_2$ (25 mol%) were added under argon atmosphere. The reaction mixture was stirred for 4–6 h at 55 °C until the 2*H*-azirine was completely consumed (monitored by TLC). Then the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (eluent: hexane/EtOAc).

(±)-Ethyl *trans*-1-benzoyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{1}): White solid, 115 mg, 69% yield, mp 102–103 °C. Silica gel TLC R_f = 0.46 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (d, *J* = 7.4 Hz, 2H), 7.56 (t, *J* = 7.3 Hz, 1H), 7.46 (t, *J* = 7.6 Hz, 2H), 7.20 (s, 1H), 4.26 – 4.12 (m, 2H), 3.53 (s, 1H), 1.71 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.96 (s, 9H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.8, 166.7, 164.5, 133.3, 132.5, 128.5, 128.0, 61.5, 51.5, 49.8, 42.9, 27.7, 14.1, 13.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_4$ 333.1814; Found 333.1817.

(2*R*,3*R*)-Ethyl 1-benzoyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate ((2*R*,3*R*)-4{1}): After column chromatography: white solid, 113 mg, 68% yield, 72% ee. The resulting solid was recrystallized from diethyl ether (2 mL) at 0 °C. White solid, 35% yield, 92% ee, $[\alpha]^{23}$ + 27.1° (c 0.7, $CHCl_3$).

(±)-Ethyl *cis*-1-benzoyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-5{1}): White solid, 7 mg, 4% yield, mp 58–88 °C. Silica gel TLC R_f = 0.67 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.13 (d, *J* = 7.6 Hz, 2H), 7.67 (t, *J* = 7.3 Hz, 1H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.27 (s, 1H), 4.24 – 4.06 (m, 2H), 3.52 (s, 1H), 1.29 (s, 3H), 1.25 (s, 9H), 1.24 – 1.21 (m, 3H, overlap with isocyanide). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.5, 166.2, 165.0, 133.6, 132.5, 128.9, 128.8, 61.5, 50.9, 50.6, 45.1, 28.2, 17.7, 14.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_4$ 333.1814; Found 333.1815.

(±)-Ethyl *trans*-3-(*tert*-butylcarbamoyl)-1-(3-methoxybenzoyl)-3-methylaziridine-2-carboxylate (*rac*-4{2}): White solid, 144 mg 79% yield, mp 100–102 °C. Silica gel TLC R_f = 0.38 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 (t, *J* = 7.8 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.23 (s, 1H), 7.21 (s, 1H), 7.12 (d, *J* = 7.9 Hz, 1H), 4.27 – 4.12 (m, 2H), 3.78 (s, 3H), 3.52 (s, 1H), 1.69 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H), 0.99 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.5, 166.6, 164.5, 159.2, 134.7, 129.7, 120.4, 118.8, 112.4, 61.5, 55.3, 51.5, 49.7, 43.0, 27.8, 14.1, 13.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{27}N_2O_5$ 363.1920; Found 363.1922.

(±)-Ethyl *trans*-3-(*tert*-butylcarbamoyl)-1-(4-hydroxybenzoyl)-3-methylaziridine-2-carboxylate (*rac*-4{3}): White solid, 98 mg, 56% yield, mp 185–187 °C. Silica gel TLC R_f = 0.12 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.17 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.12 (s, 1H), 6.79 (d, *J* = 8.5 Hz, 2H), 4.25 – 4.12 (m, 2H), 3.54 (s, 1H), 1.67 (s, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 0.98 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.0, 166.9, 164.5, 161.5, 130.4, 124.1, 115.1, 61.3, 51.4, 49.7, 42.7, 27.8, 14.1, 13.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_5$ 349.1763; Found 349.1767.

(±)-Ethyl *trans*-3-(*tert*-butylcarbamoyl)-1-(2-chlorobenzoyl)-3-methylaziridine-2-carboxylate (*rac*-4{4}): White solid, 103 mg, 61% yield, mp 102–103 °C. Silica gel TLC R_f = 0.50 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 (d, *J* = 7.6 Hz, 1H), 7.50 – 7.45 (m, 2H), 7.44 – 7.37 (m, 1H), 7.13 (s, 1H), 4.24 – 4.11 (m, 2H), 3.48 (s, 1H), 1.60 (s, 3H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.02 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.3, 166.3, 164.7, 132.8, 132.5, 132.0, 131.0, 130.7, 127.0, 61.5, 51.5, 49.3, 43.5, 27.9, 14.1, 13.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{24}ClN_2O_4$ 367.1425; Found 367.1427.

(±)-Ethyl *trans*-3-(*tert*-butylcarbamoyl)-3-methyl-1-(2-phenylacetyl)aziridine-2-carboxylate (*rac*-4{5}): White solid, 119 mg, 69% yield, mp 107–108 °C. Silica gel TLC R_f = 0.44 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.33 – 7.28 (m, 2H), 7.28 (s, 1H), 7.25 – 7.18 (m, 3H), 4.24 – 4.05 (m, 2H), 3.56 (q, *J* = 16.0 Hz, 2H), 3.23 (s, 1H), 1.38 (s, 3H), 1.29 (s, 9H), 1.19 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.2, 166.4, 165.8, 134.6, 129.9, 128.2, 126.7, 61.3,

51.7, 49.0, 43.5, 42.66, 28.2, 14.1, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{27}N_2O_4$ 347.1971; Found 347.1972.

(±)-Ethyl *trans*-3-(*tert*-butylcarbamoyl)-3-methyl-1-((E)-3-(3,4,5-trimethoxyphenyl) acryloyl)aziridine-2-carboxylate (*rac*-4{6}): White solid, 135 mg, 60%, mp 131–132 °C. Silica gel TLC R_f = 0.41 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.37 (d, J = 15.9 Hz, 1H), 7.31 (s, 1H), 7.01 (s, 2H), 6.60 (d, J = 15.9 Hz, 1H), 4.26 – 4.13 (m, 2H), 3.80 (s, 6H), 3.68 (s, 3H), 3.52 (s, 1H), 1.64 (s, 3H), 1.26 – 1.20 (m, 3H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.4, 166.7, 164.8, 153.1, 142.2, 139.5, 129.9, 120.6, 106.1, 61.3, 60.2, 56.2, 51.6, 49.0, 42.8, 28.1, 14.1, 13.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{33}N_2O_7$ 449.2288; Found 449.2294.

(±)-Ethyl *trans*-3-(*tert*-butylcarbamoyl)-3-methyl-1-nicotinoylaziridine-2-carboxylate (*rac*-4{7}): White solid, 47 mg, 28%, mp 114–116 °C. Silica gel TLC R_f = 0.29 (hexane/EtOAc = 1/2). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 (s, 1H), 8.73 (d, J = 3.7 Hz, 1H), 8.07 (d, J = 7.9 Hz, 1H), 7.51 (dd, J = 7.6, 4.9 Hz, 1H), 7.32 (s, 1H), 4.27 – 4.13 (m, 2H), 3.54 (s, 1H), 1.72 (s, 3H), 1.29 – 1.17 (m, 3H), 0.97 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.8, 166.4, 164.5, 153.0, 148.6, 135.6, 129.2, 123.8, 61.6, 51.6, 50.0, 43.11, 27.7, 14.1, 13.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{24}N_3O_4$ 334.1767; Found 334.1767.

(±)-Ethyl *trans*-1-acetyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{8}): White solid, 102 mg, 75%, mp 101–102 °C. Silica gel TLC R_f = 0.31 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.31 (s, 1H), 4.25 – 4.07 (m, 2H), 3.28 (s, 1H), 1.91 (s, 3H), 1.53 (s, 3H), 1.27 (s, 9H), 1.21 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 178.0, 166.5, 165.5, 61.3, 51.7, 48.3, 42.9, 28.2, 23.9, 14.1, 13.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{23}N_2O_4$ 271.1658; Found 271.1657.

(±)-Ethyl *trans*-3-(*tert*-butylcarbamoyl)-1-(2-chloroacetyl)-3-methylaziridine-2-carboxylate (*rac*-4{9}): White solid, 84 mg, 55%, mp 93–94 °C. Silica gel TLC R_f = 0.51 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.43 (s, 1H), 4.28 – 4.10 (m, 4H), 3.20 (s, 1H), 1.60 (s, 3H), 1.26 (s, 9H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.7, 166.1, 165.8, 61.5, 51.7, 50.5, 44.0, 42.6, 28.1, 14.1, 13.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{22}ClN_2O_4$ 305.1268; Found 305.1269.

(±)-Ethyl *trans*-3-(*tert*-butylcarbamoyl)-3-methyl-1-(2,2,2-trifluoroacetyl)aziridine-2-carboxylate (*rac*-4{10}): White solid, 87 mg, 54%, mp 94–95 °C. Silica gel TLC R_f = 0.53 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (s, 1H), 4.31 – 4.12 (m, 2H), 3.30 (s, 1H), 1.64 (s, 3H), 1.25 (s, 9H), 1.24 – 1.20 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 166.08 (q, J = 36.6 Hz), 165.5, 164.9, 115.33 (q, J = 287.5 Hz), 62.0, 54.0, 52.1, 41.6, 27.9, 14.0, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{13}H_{20}F_3N_2O_4$ 325.1375; Found 325.1376.

(±)-Ethyl *trans*-1-benzoyl-3-methyl-3-((2,4,4-trimethylpentan-2-yl)carbamoyl)aziridine-2-carboxylate (*rac*-4{11}): White solid, 151 mg, 78%, mp 83–84 °C. Silica gel TLC R_f = 0.61 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (d, J = 7.7 Hz, 2H), 7.55 (t, J = 7.2 Hz, 1H), 7.45 (t, J = 7.5 Hz, 2H), 7.03 (s, 1H), 4.29 – 4.09 (m, 2H), 3.42 (s, 1H), 1.71 (s, 3H), 1.55 (d, J = 14.7 Hz, 1H), 1.35 (d, J = 14.7 Hz, 1H), 1.22 (t, J = 7.0 Hz, 3H), 1.06 (s, 3H), 0.99 (s, 3H), 0.80 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.9, 166.6, 164.4, 133.7, 132.4, 128.5, 127.9, 61.4, 55.3, 50.0, 49.8, 42.8, 31.2, 31.1, 28.4, 28.2, 14.1, 13.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{33}N_2O_4$ 389.2440; Found 389.2439.

(±)-Ethyl *trans*-1-benzoyl-3-(cyclohexylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{12}): White solid, 127 mg, 71%, mp 166–167 °C. Silica gel TLC R_f = 0.67 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.87 (d, J = 7.9 Hz, 1H), 7.71 (d, J = 7.2 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 7.46 (t, J = 7.6 Hz, 2H), 4.26 – 4.12 (m, 2H), 3.54 (s, 1H), 3.25 (ddd, J = 14.9, 11.5, 5.9 Hz, 1H), 1.69 (s, 3H), 1.58 (dd, J = 22.6, 12.7 Hz, 2H), 1.46 (d, J = 9.3 Hz, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.20 – 0.82 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.7, 166.6, 164.3, 133.3, 132.5, 128.6, 127.9, 61.5, 49.3, 49.0, 43.1, 31.5, 31.4, 25.1, 24.8, 24.7, 14.1, 13.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{27}N_2O_4$ 359.1971; Found 359.1972.

(±)-Ethyl *trans*-1-benzoyl-3-(benzylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{13}): White solid, 106 mg, 58%, mp 121–123 °C. Silica gel TLC R_f = 0.59 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.82 (t, J = 5.4 Hz, 1H), 7.76 (d, J = 7.8 Hz, 2H), 7.63 (t, J = 7.3 Hz, 1H), 7.49 (t, J = 7.4 Hz, 2H), 7.19 – 7.10 (m, 3H), 6.80 (d, J = 3.8 Hz, 2H), 4.28 (dd, J = 15.2, 6.6 Hz, 1H), 4.25 – 4.16 (m, 2H), 3.96 (dd, J = 15.2, 5.0 Hz, 1H), 3.56 (s, 1H), 1.74 (s, 3H), 1.23 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.7, 166.4, 165.8, 138.5, 133.4, 132.7, 128.70, 128.2, 128.0, 126.7,

126.7, 61.5, 49.0, 43.3, 42.9, 14.1, 13.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{23}N_2O_4$ 367.1658; Found 367.1659.

(±)-Ethyl *trans*-1-benzoyl-3-methyl-3-((3,4,5-trimethoxyphenyl)carbamoyl)aziridine-2-carboxylate (*rac*-4{14}): White solid, 84 mg, 38%, mp 140–141 °C. Silica gel TLC R_f = 0.36 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.70 (s, 1H), 7.82 (d, J = 7.4 Hz, 2H), 7.58 (t, J = 7.1 Hz, 1H), 7.49 (t, J = 7.3 Hz, 2H), 6.66 (s, 2H), 4.21 (dd, J = 13.5, 6.5 Hz, 2H), 3.68 (s, 1H), 3.63 (s, 6H), 3.57 (s, 3H), 1.83 (s, 3H), 1.23 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.3, 166.2, 164.6, 152.5, 134.5, 133.5, 133.3, 132.8, 128.7, 128.0, 99.5, 61.6, 60.1, 55.8, 49.4, 43.6, 14.1, 13.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{27}N_2O_7$ 443.1818; Found 443.1819.

(±)-Ethyl *trans*-1-benzoyl-3-methyl-3-((4-nitrophenyl)carbamoyl)aziridine-2-carboxylate (*rac*-4{15}): Pale yellow solid, 120 mg, 60%, mp 141–143 °C. Silica gel TLC R_f = 0.66 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.31 (s, 1H), 8.16 (d, J = 9.1 Hz, 2H), 7.84 (d, J = 7.4 Hz, 2H), 7.73 (d, J = 9.1 Hz, 2H), 7.57 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.6 Hz, 2H), 4.28 – 4.12 (m, 2H), 3.75 (s, 1H), 1.87 (s, 3H), 1.22 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.0, 166.0, 165.9, 143.9, 143.2, 133.2, 132.8, 128.8, 128.0, 124.5, 120.8, 61.7, 49.5, 43.75, 14.0, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{20}N_3O_6$ 398.1352; Found 398.1352.

(±)-Ethyl *trans*-3-methyl-1-(2-phenylacetyl)-3-((2,4,4-trimethylpentan-2-yl)carbamoyl)aziridine-2-carboxylate (*rac*-4{16}): White solid, 149 mg, 77%, mp 95–96 °C. Silica gel TLC R_f= 0.59 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.32 – 7.25 (m, 2H), 7.24 – 7.19 (m, 3H), 7.14 (s, 1H), 4.21 – 4.02 (m, 2H), 3.57 (q, J = 16.0 Hz, 2H), 3.14 (s, 1H), 1.84 (d, J = 14.7 Hz, 1H), 1.56 (d, J = 14.7 Hz, 1H), 1.39 (s, 3H), 1.34 (s, 6H), 1.18 (t, J = 7.0 Hz, 3H), 0.94 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.2, 166.3, 165.6, 134.7, 129.9, 128.2, 126.6, 61.3, 55.5, 50.0, 49.3, 43.7, 42.5, 31.4, 31.2, 29.1, 28.6, 14.1, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{35}N_2O_4$ 403.2597; Found 403.2599.

(±)-Ethyl *trans*-3-methyl-3-(pentylcarbamoyl)-1-(2-phenylacetyl)aziridine-2-carboxylate (*rac*-4{17}): White solid, 142 mg, 79%, mp 90–91 °C. Silica gel TLC R_f= 0.30 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.27 (t, J = 4.5 Hz, 1H), 7.28 (t, J = 7.3 Hz, 2H), 7.24 – 7.17 (m, 3H), 4.23 – 3.98 (m, 2H), 3.63 – 3.43 (m, 2H), 3.29 (s, 1H), 3.22 – 2.97 (m, 2H), 1.51 – 1.40 (m, 2H), 1.34 (s, 3H), 1.32 – 1.22 (m, 4H), 1.19 (t, J = 7.1 Hz, 3H), 0.84 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.1, 166.3, 166.1, 134.5, 129.9, 128.2, 126.7, 61.3, 48.1, 43.4, 43.0, 28.6, 28.5, 21.8, 14.05, 13.9, 13.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{29}N_2O_4$ 361.2127; Found 361.2130.

(±)-Ethyl *trans*-1-acetyl-3-(cyclohexylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{18}): White solid, 101 mg, 68%, mp 97–98 °C. Silica gel TLC R_f = 0.55 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, J = 7.5 Hz, 1H), 4.24 – 4.06 (m, 2H), 3.54 (d, J = 7.5 Hz, 1H), 3.31 (s, 1H), 1.89 (s, 3H), 1.72 (d, J = 40.2 Hz, 4H), 1.56 (d, J = 12.4 Hz, 1H), 1.50 (s, 3H), 1.32 – 1.17 (m,4H), 1.20 (t, J = 6.6 Hz, 3H), 1.15 – 0.97 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 178.0, 166.4, 165.1, 61.3, 49.3, 47.7, 43.1, 32.1, 31.8, 25.1, 24.9, 24.9, 23.8, 14.1, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{25}N_2O_4$ 297.1814; Found 297.1815.

(±)-Ethyl *trans*-3-(cyclohexylcarbamoyl)-3-methyl-1-(2-phenylacetyl)aziridine-2-carboxylate (*rac*-4{19}): White solid, 112 mg, 60%, mp 101–102 °C. Silica gel TLC R_f = 0.35 (hexane/EtOAc = 2/1), ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (d, J = 7.6 Hz, 1H), 7.28 (t, J = 7.2 Hz, 2H), 7.25 – 7.15 (m, 3H), 4.22 – 3.96 (m, 2H), 3.62 – 3.56 (m, 1H), 3.54 (s, 2H), 3.28 (s, 1H), 1.79 – 1.63 (m, 4H), 1.60 – 1.51 (m, 1H), 1.32 (s, 3H), 1.29 – 1.21 (m, 4H), 1.19 (t, J = 7.1 Hz, 3H), 1.14 – 1.00 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.2, 166.3, 165.3, 134.6, 129.9, 128.2, 126.7, 61.3, 49.4, 48.3, 43.5, 43.0, 32.1, 31.9, 25.2, 24.9, 14.1, 13.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{29}N_2O_4$ 373.2127; Found 373.2130.

(±)-Ethyl *trans*-3-(cyclohexylcarbamoyl)-3-methyl-1-(2,4,6-trimethylbenzoyl)aziridine-2-carboxylate (*rac*-4{20}): White solid, 160 mg, 80% yield, mp 143–144 °C. Silica gel TLC R_f = 0.61 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.81 (d, J = 7.6 Hz, 1H), 6.82 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.57 (s, 1H), 3.50 – 3.40 (m, 1H), 2.28 (s, 6H), 2.19 (s, 3H), 1.61 (dd, J = 32.6, 16.0 Hz, 3H), 1.57 – 1.41 (m, 5H), 1.29 (s, 2H), 1.20 – 1.13 (m, 4H), 1.15 – 0.98 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.8, 166.3, 164.1, 138.8, 135.8, 132.2, 128.6, 61.4, 49.2, 48.3, 42.6, 31.8, 25.2, 24.9, 24.8, 20.6, 20.0, 14.0, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{33}N_2O_4$ 401.2440; Found 401.2442.

(±)-Ethyl *trans*-3-(cyclohexylcarbamoyl)-1-(3-fluorobenzoyl)-3-methylaziridine-2-carboxylate (*rac*-4{21}): White solid, 145 mg, 77% yield, mp 165–167 °C. Silica gel TLC R_f = 0.39 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.94 (d, J = 7.9 Hz, 1H), 7.58 –

7.49 (m, 2H), 7.45 – 7.39 (m, 2H), 4.27 – 4.14 (m, 2H), 3.54 (s, 1H), 3.29 – 3.20 (m, 1H), 1.69 (s, 3H), 1.65 – 1.53 (m, 2H), 1.48 (s, 2H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.19 – 0.82 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.7, 166.4, 164.3, 161.9 (d, *J* = 245.0 Hz), 135.7 (d, *J* = 6.8 Hz), 130.9 (d, *J* = 7.7 Hz), 124.0, 119.5 (d, *J* = 21.1 Hz), 114.3 (d, *J* = 22.7 Hz), 61.6, 49.4, 49.1, 43.2, 31.5, 25.0, 24.8, 24.7, 14.1, 13.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{26}FN_2O_4$ 377.1877; Found 377.1876.

(±)-Ethyl *trans*-3-(benzylcarbamoyl)-3-methyl-1-(2-phenylacetyl)aziridine-2-carboxylate (*rac*-4{22}): White solid, 127 mg, 67% yield, mp 123–125 °C. Silica gel TLC R_f = 0.25 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, $CDCl_3$-d_1) δ 7.51 – 6.85 (m, 10H), 6.35 – 6.26 (m, 1H), 4.64 – 4.28 (m, 2H), 4.27 – 4.08 (m, 2H), 3.70 (dd, *J* = 39.2, 16.5 Hz, 2H), 3.37 (s, 1H), 1.45 (s, 3H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$-d_1) δ 177.9, 166.8, 165.6, 136.8, 133.5, 129.5, 128.5, 128.1, 127.5, 127.5, 126.6, 61.6, 47.0, 43.9, 43.8, 43.5, 13.7, 11.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{25}N_2O_4$ 381.1814; Found 381.1814.

(±)-Ethyl *trans*-3-(benzylcarbamoyl)-1-(3-methoxybenzoyl)-3-methylaziridine-2-carboxylate (*rac*-4{23}): White solid, 104 mg, 58% yield, mp 78–79 °C. Silica gel TLC R_f = 0.59 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.84 (s, 1H), 7.45 – 7.29 (m, 2H), 7.27 – 7.17 (m, 2H), 7.17 – 7.08 (m, 3H), 6.80 (s, 2H), 4.30 (d, *J* = 12.8 Hz, 1H), 4.25 – 4.15 (m, 2H), 3.96 (d, *J* = 13.6 Hz, 1H), 3.76 (s, 3H), 3.55 (s, 1H), 1.72 (s, 3H), 1.23 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.4, 166.4, 165. 7, 159.2, 138.5, 134. 7, 129.9, 128.1, 126.7, 126.7, 120.3, 118.9, 112. 5, 61.6, 55.3, 49.0, 43.3, 42.9, 14.1, 13.8. HRMS (ESI) m/z: $[M+H]^+$ Calculated for $C_{22}H_{25}N_2O_5$ 397.1763; Found 397.1764.

(±)-Ethyl *trans*-1-acetyl-3-methyl-3-((3,4,5-trimethoxyphenyl)carbamoyl)aziridine-2-carboxylate (*rac*-4{24}): White solid, 27 mg, 22% yield, mp 140–142 °C. Silica gel TLC R_f = 0.41 (hexane/EtOAc = 1/2). ^{1}H NMR (500 MHz, $CDCl_3$-d_1) δ 7.96 (s, 1H), 6.81 (s, 2H), 4.27 (q, *J* = 7.4 Hz, 2H), 3.83 (s, 6H), 3.80 (s, 3H), 3.45 (s, 1H), 2.18 (s, 3H), 1.75 (s, 3H), 1.31 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$-d_1) δ 176.4, 165.4, 165.2, 152.9, 134.8, 132.4, 97.3, 62.0, 60.5, 55.7, 47.3, 43.6, 24.0, 13.7, 10.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_7$ 381.1662; Found 381.1662.

(±)-Ethyl *trans*-3-methyl-1-(2-phenylacetyl)-3-((3,4,5-trimethoxyphenyl)carbamoyl) aziridine-2-carboxylate (*rac*-4{25}): Colorless oil, 81 mg, 36% yield. Silica gel TLC R_f = 0.40 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, $CDCl_3$-d_1) δ 7.76 (s, 1H), 7.36 – 7.20 (m, 5H), 6.73 (s, 2H), 4.23 (dd, *J* = 13.5, 6.6 Hz, 2H), 3.81 (s, 6H), 3.79 (s, 3H), 3.78 – 3.68 (m, 2H), 3.37 (s, 1H), 1.60 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$-d_1) δ 177.5, 165.3, 165.1, 152.9, 134.8, 133.4, 132.5, 129.4, 128.2, 126.8, 97.3, 60.5, 55.7, 47.4, 43.6, 29.2, 13.7, 11.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{29}N_2O_7$ 457.1975; Found 457.1977.

(±)-Ethyl *trans*-3-methyl-1-(4-(trifluoromethyl)benzoyl)-3-((3,4,5-trimethoxyphenyl) carbamoyl)aziridine-2-carboxylate (*rac*-4{26}): White solid, 74 mg, 29% yield, mp 149–150 °C. Silica gel TLC R_f = 0.44 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.75 (s, 1H), 8.01 (d, *J* = 7.6 Hz, 2H), 7.87 (d, *J* = 7.6 Hz, 2H), 6.66 (s, 2H), 4.22 (d, *J* = 6.7 Hz, 2H), 3.70 (s, 1H), 3.63 (s, 6H), 3.57 (s, 3H), 1.85 (s, 3H), 1.22 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 173.5, 166.0, 164.6, 152.5, 137.1, 134.6, 133.4, 132.2 (q, *J* = 31.8 Hz) 128.8, 125.8, 99.35, 61.8, 60.1, 55.7, 49.9, 43.7, 14.0, 13.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{26}F_3N_2O_7$ 511.1692; Found 511.1688.

(±)-Ethyl *trans*-1-(2-chloroacetyl)-2,3-dimethyl-3-((4-nitrophenyl)carbamoyl)aziridine-2-carboxylate (*rac*-4{27}): Light-yellow solid, 104 mg, 56% yield, mp 148–151 °C. Silica gel TLC R_f = 0.28 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.41 (s, 1H), 8.24 (d, *J* = 9.1 Hz, 2H), 7.89 (d, *J* = 9.2 Hz, 2H), 4.41 (q, *J* = 15.3 Hz, 2H), 4.27 – 4.17 (m, 2H), 3.52 (s, 1H), 1.78 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.1, 166.5, 165.6, 144.0, 143.3, 124.7, 120.9, 61.8, 50.1, 44.1, 43.0, 14.1, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{15}H_{17}ClN_3O_6$ 370.0806; Found 370.0804.

(±)-Ethyl *trans*-1-(3-fluorobenzoyl)-3-methyl-3-((4-nitrophenyl)carbamoyl)aziridine-2-carboxylate (*rac*-4{28}): Light-yellow solid, 59 mg, 28% yield, mp 145–146 °C. Silica gel TLC R_f = 0.29 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.34 (s, 1H), 8.17 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.68 (d, *J* = 7.0 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.44 (t, *J* = 7.1 Hz, 1H), 4.28 – 4.12 (m, 2H), 3.79 (s, 1H), 1.86 (s, 3H), 1.21 (t, *J* = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.83, 165.82 (d, *J* = 10.4 Hz), 162.93, 160.98, 143.89, 143.20, 135.65 (d, *J* = 6.9 Hz), 131.09 (d, *J* = 7.6 Hz), 124.58, 124.10, 120.73, 119.80 (d, *J* = 21.1 Hz), 114.48 (d, *J* = 22.9 Hz), 61.82, 49.66, 43.74, 14.01, 13.26. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{19}FN_3O_6$ 416.1258; Found 416.1257.

(±)-t*ert*-Butyl *trans*-1-benzoyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{29}): White

solid, 110 mg, 61% yield, mp 167–168 °C. Silica gel TLC R_f = 0.75 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.73 (d, J = 7.4 Hz, 2H), 7.55 (t, J = 7.1 Hz, 1H), 7.46 (t, J = 7.3 Hz, 2H), 7.13 (s, 1H), 3.44 (s, 1H), 1.70 (s, 3H), 1.43 (s, 9H), 0.96 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.7, 165.7, 164.7, 133.4, 132.5, 128.5, 128.0, 82.4, 51.4, 49.2, 43.7, 27.8, 27.7, 13.3. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{29}N_2O_4$ 361.2127; Found 361.2127.

(±)-t*ert*-Butyl *trans*-1-acetyl-3-(cyclohexylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{30}): White solid, 87 mg, 54% yield, mp 108–109 °C. Silica gel TLC R_f = 0.44 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.93 (d, J = 7.6 Hz, 1H), 3.59 – 3.44 (m, 1H), 3.22 (s, 1H), 1.87 (s, 3H), 1.75 – 1.64 (m, 4H), 1.61 – 1.53 (m, 1H), 1.50 (s, 3H), 1.42 (s, 9H), 1.35 – 1.13 (m, 4H), 1.13 – 0.94 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 178,0, 165.6, 165.3, 82.2, 49.3, 47.4, 43.8, 32.1, 31.8, 27.7, 25.1, 24.9, 24.9, 23.8, 13.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{17}H_{29}N_2O_4$ 325.2127; Found 325.2129.

(±)-t*ert*-Butyl *trans*-1-benzoyl-3-(benzylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{31}): White solid, 42 mg, 22% yield, mp 153–154 °C. Silica gel TLC R_f = 0.54 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.78 (t, J = 5.2 Hz, 1H), 7.76 (d, J = 7.4 Hz, 2H), 7.62 (t, J = 7.2 Hz, 1H), 7.48 (t, J = 7.5 Hz, 2H), 7.18 – 7.08 (m, 3H), 6.86 – 6.72 (m, 2H), 4.29 (dd, J = 15.1, 6.6 Hz, 1H), 3.96 (dd, J = 15.1, 4.8 Hz, 1H), 3.30 (s, 1H), 1.72 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 174.5, 165.9, 165.5, 138.5, 133.5, 132. 7, 128. 7, 128.2, 127.9, 126.7, 82.5, 48.6, 44.1, 42.9, 27.7, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{27}N_2O_4$ 395.1971; Found 395.1973.

(±)-t*ert*-Butyl *trans*-3-methyl-3-((3,4,5-trimethoxyphenyl)carbamoyl)-1-(2,4,6-trimethylbenzoyl)aziridine-2-carboxylate (*rac*-4{32}): White solid, 52 mg, 20% yield, mp 94–95 °C. Silica gel TLC R_f = 0.42 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.66 (s, 1H), 6.91 (s, 2H), 6.83 (s, 2H), 3.71 (s, 6H), 3.61 (s, 3H), 3.57 (s, 1H), 2.31 (s, 6H), 2.18 (s, 3H), 1.67 (s, 3H), 1.40 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.9, 165.2, 164.3, 152.5, 138.9, 135.9, 134.4, 133.9, 132.1, 128.8, 99.2, 82.5, 60.1, 55.8, 48.7, 43.5, 27.6, 20.6, 20.0, 13.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{28}H_{37}N_2O_7$ 513.2601; Found 513.2592.

Mixture of (±)-Ethyl *trans*-1-benzoyl-3-(*tert*-butylcarbamoyl)-2,3-dimethylaziridine-2-carboxylate and (±)-Ethyl *cis*-1-benzoyl-3-(*tert*-butylcarbamoyl)-2,3-dimethylaziridine-2-carboxylate (*rac*-4{33}+5{33}): Yellow oil, 95 mg, 55% combined yield. Silica gel TLC R_f = 0.51 and R_f = 0.46 (diastereomers, hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) major (*trans*) diastereomer: δ 7.79 (d, J = 7.2 Hz, 2H), 7.54 (t, J = 7.5 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.40 (s, 1H), 3.96 (dddd, J = 17.9, 10.8, 7.1, 3.8 Hz, 2H), 1.57 (s, 3H), 1.54 (s, 3H), 1.26 (s, 9H), 1.00 (t, J = 7.1 Hz, 1H). minor (*cis*) diastereomer: δ 8.03 – 7.99 (m, 2H), 7.62 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.11 (s, 1H), 4.19 – 4.04 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H), 1.23 (s, 9H), 1.19 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ mixtures of diastereomers: 172.5, 172.4, 168.2, 167.2, 166.8, 166.3, 134.7, 133.6, 133.1, 132.1, 128.7, 128.5, 128.3, 127.7, 61.6, 61.6, 51.0, 50.9, 50.5, 49.8, 28.3, 28.1, 16.0, 13.9, 13.9, 13.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{27}N_2O_4$ 347.1971; Found 347.1971.

(±)-Ethyl *trans*-1-benzoyl-3-(cyclohexylcarbamoyl)-2,3-dimethylaziridine-2-carboxylate (*rac*-4{34}): White solid, 58 mg, 31% yield, mp 99–100 °C. Silica gel TLC R_f = 0.40 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.91 (d, J = 8.3 Hz, 1H), 7.77 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.3 Hz, 1H), 7.47 (t, J = 7.5 Hz, 2H), 4.10 – 3.87 (m, 2H), 3.62 – 3.47 (m, 1H), 1.70 – 1.61 (m, 4H), 1.55 (s, 3H), 1.54 (s, 4H), 1.32 – 1.16 (m, 4H) 1.10 – 1.02 (m, 1H), 1.01 (t, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.6, 167.3, 166.2, 134.9, 132.1, 128.4, 127.7, 61.7, 48.3, 32.2, 25.2,24.9, 24.9, 15.7, 13.8, 12.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{29}N_2O_4$ 373.2127; Found 373.2129.

Mixture of (±)-ethyl *trans*-3-(benzylcarbamoyl)-1-(3-methoxybenzoyl)-2,3-dimethylaziridine-2-carboxylate and (±)-ethyl *cis*-3-(benzylcarbamoyl)-1-(3-methoxybenzoyl)-2,3-dimethylaziridine-2-carboxylate (*rac*-4{35}+5{35}): Yellow oil, 84 mg, 41% combined yield. Alumina TLC R_f = 0.22 and R_f = 0.31 (diastereomers, hexane/EtOH = 20/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ mixture of diastereomers: 8.73 (t, J = 6.2 Hz, 1H), 8.55 (t, J = 6.1 Hz, 1H), 7.63 – 7.58 (m, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.45 – 7.40 (m, 1H), 7.39 (t, J = 7.8 Hz, 2H), 7.34 (s, 1H), 7.34 – 7.30 (m, 1H), 7.30 – 7.21 (m, 8H), 7.21 – 7.07 (m, 3H), 4.31 – 4.26 (m, 2H), 4.24 (d, J = 6.1 Hz, 2H), 3.99 (q, J = 7.1 Hz, 2H), 3.92 (qt, J = 6.7, 3.3 Hz, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 1.58 (s, 3H), 1.53 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ mixtures of diastereomers: 172.4, 172.3, 168.1, 167.3, 167.3, 167.2, 159.2, 159.1, 139.2, 139.2, 136.2, 135.1, 129.8, 129.7, 128.3, 128.2, 127.6, 127.5, 126.9, 126.8, 120.6, 120.0, 119.2, 118.0, 113.0, 112.5, 61.8, 61.3, 55.3, 55.3, 50.6,

49.7, 42.5, 42.5, 15.7, 14.1, 13.8, 13.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{27}N_2O_5$ 411.1920; Found 411.1924.

(±)-Ethyl *trans*-1-benzoyl-2-benzyl-3-(tert-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{36}): Colorless oil, 36 mg, 17% yield. Silica gel TLC R_f = 0.66 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.69 – 7.56 (m, 3H), 7.46 (t, J = 7.6 Hz, 1H), 7.39 – 7.33 (m, 2H), 7.32 – 7.21 (m, 5H), 4.03 – 3.88 (m, 2H), 3.51 (d, J = 14.8 Hz, 1H), 2.81 (d, J = 14.9 Hz, 1H), 1.49 (s, 3H), 1.30 (s, 9H), 0.95 (t, J = 6.9 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.1, 166.6, 166.3, 136.8, 134.5, 131.9, 129.5, 128.3, 128.1, 127.9, 126.7, 61.5, 52.5, 52.4, 51.2, 35.2, 28.4, 14.5, 13.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{31}N_2O_4$ 423.2284; Found 423.2287.

(±)-Ethyl *cis*-1-benzoyl-2-benzyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-5{36}): Colorless oil, 49 mg, 23% yield. Silica gel TLC R_f = 0.71 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 (d, J = 7.1 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.9 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.27 – 7.22 (m, 2H), 7.22 – 7.15 (m, 1H), 7.08 (s, 1H), 3.88 – 3.74 (m, 2H), 3.28 – 3.10 (m, 2H), 1.42 (s, 3H), 1.23 (d, J = 2.7 Hz, 9H), 0.82 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 172.6, 166.8, 166.2, 135.9, 133.8, 133.1, 129.5, 128.7, 128.4, 127.9, 126.6, 61.0, 53.2, 50.9, 50.6, 33.9, 28.1, 14.8, 13.4. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{31}N_2O_4$ 423.2284; Found 423.2287.

(±)-*trans*-1-Benzoyl-*N*-(*tert*-butyl)-2,3-diphenylaziridine-2-carboxamide (*rac*-4{37}): White solid, 139 mg, 70% yield, mp 126–127 °C. Silica gel TLC R_f = 0.90 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (d, J = 7.7 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.44 (t, J = 7.6 Hz, 2H), 7.35 – 7.26 (m, 4H), 7.28 – 7.20 (m, 1H), 7.13 (bs, 5H), 5.90 (s, 1H), 4.58 (s, 1H), 1.00 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.7, 164.3, 133.8, 132.9, 132.7, 132.0, 129.4, 128.6, 128.5, 128.4, 128.1, 128.0, 127.7, 127.4, 57.6, 51.4, 49.6, 27.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{26}H_{27}N_2O_2$ 399.2073; Found 399.2074.

(±)-*trans*-1-Acetyl-*N*-(*tert*-butyl)-2,3-diphenylaziridine-2-carboxamide (*rac*-4{38}): White solid, 102 mg, 61% yield, mp 116–117 °C. Silica gel TLC R_f = 0.77 (hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30 – 7.22 (m, 3H), 7.22 – 7.18 (m, 2H), 7.11 – 7.06 (m, 3H), 7.04 – 6.97 (m, 2H), 5.80 (s, 1H), 4.35 (s, 1H), 2.13 (s, 3H), 1.18 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.6, 165.1, 134.1, 132.1, 129.4, 128.6, 128.5, 127.8, 127.5, 127.2, 57.0, 51.6, 48.3, 28.1, 23.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{25}N_2O_2$ 337.1916; Found 337.1916.

(±)-*trans*-*N*-Cyclohexyl-2,3-diphenyl-1-(2,4,6-trimethylbenzoyl)aziridine-2-carboxamide (*rac*-4{39}): White solid, 65 mg, 28% yield, mp 135–136 °C. Silica gel TLC R_f = 0.94 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.30 – 7.20 (m, 3H), 7.18 – 7.12 (m, 2H), 7.02 (q, J = 6.9, 6.1 Hz, 3H), 6.91 – 6.84 (m, 2H), 6.81 (s, 2H), 6.51 (d, J = 8.2 Hz, 1H), 4.54 (s, 1H), 3.75 – 3.60 (m, 1H), 2.37 (s, 6H), 2.16 (s, 3H), 1.72 – 1.40 (m, 5H), 1.30 – 1.09 (m, 5H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 177.4, 164.6, 138.1, 134.4, 133.6, 133.4, 132.3, 129.5, 128.4, 128.3, 127.7, 127.6, 127.1, 61.7, 56.6, 48.8, 48.7, 31.7, 31.6, 25.0, 24.5, 20.6, 19.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{31}H_{35}N_2O_2$ 469.2766; Found 469.2761.

(±)-*trans*-2,3-Diphenyl-1-(2-phenylacetyl)-*N*-(3,4,5-trimethoxyphenyl)aziridine-2-carboxamide (*rac*-4{40}): White solid, 114 mg, 43% yield, mp 144–146 °C. Silica gel TLC R_f = 0.36 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (s, 1H), 7.33 – 7.19 (m, 10H), 7.10 – 7.07 (m, 3H), 7.04 – 6.99 (m, 2H), 6.96 (s, 2H), 4.66 (s, 1H), 3.95 (d, J = 16.0 Hz, 1H), 3.81 (d, J = 16.1 Hz, 1H), 3.69 (s, 6H), 3.59 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 180.4, 165.0, 152.5, 134.7, 134.5, 133.9, 133.7, 131.4, 129.8, 129.7, 128.5, 128.4, 128.2, 127.7, 127.6, 127.4, 127.3, 126.6, 99.2, 60.1, 57.6, 55.9, 49.4, 42.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{32}H_{31}N_2O_5$ 523.2233; Found 523.2227.

(±)-*trans*-1-Benzoyl-2-benzyl-*N*-(*tert*-butyl)-3-phenylaziridine-2-carboxamide (*rac*-4{41}): White solid, 138 mg, 67% yield, mp 146–147 °C. Silica gel TLC R_f = 0.82 (hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (d, J = 7.5 Hz, 2H), 7.57 – 7.52 (m, 1H), 7.51 (d, J = 7.5 Hz, 2H), 7.44 – 7.35 (m, 4H), 7.33 (t, J = 7.1 Hz, 1H), 7.20 – 7.10 (m, 3H), 7.03 (d, J = 7.0 Hz, 2H), 6.92 (s, 1H), 4.41 (s, 1H), 3.64 (d, J = 16.3 Hz, 1H), 2.97 (d, J = 16.2 Hz, 1H), 0.87 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 176.3, 164.3, 136.4, 134.6, 133.3, 132.5, 128.6, 128.5, 128.4, 128.4, 128.2, 128.0, 126. 5, 55.4, 51.0, 46.5, 32.0, 27.8. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{27}H_{29}N_2O_2$ 413.2229; Found 413.2231.

(±)-*trans*-1-Acetyl-2-benzyl-*N*-(*tert*-butyl)-3-phenylaziridine-2-carboxamide (*rac*-4{42}): White solid, 109 mg, 62% yield, mp 151–152 °C. Silica gel TLC R_f = 0.57 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.52 (s, 1H), 7.45 – 7.37 (m, 4H), 7.37 – 7.30 (m, 1H), 7.31 – 7.22 (m, 4H), 7.23 – 7.17 (m,

1H), 3.79 (s, 1H), 3.25 (d, *J* = 15.1 Hz, 1H), 2.44 (d, *J* = 15.2 Hz, 1H), 1.65 (s, 3H), 1.22 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 180.2, 166.2, 137.2, 134.6, 129.3, 128.3, 128.2, 127.9, 127.8, 126.7, 55.4, 51.4, 46.7, 32.6, 28.3, 24.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{27}N_2O_2$ 351.2073; Found 351.2074.

(±)-*trans*-2-Benzyl-*N*-cyclohexyl-3-phenyl-1-(2,4,6-trimethylbenzoyl)aziridine-2-carboxamide (*rac*-4{43}): White solid, 96 mg, 40% yield, mp 132–133 °C. Silica gel TLC R_f = 0.75 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61 (d, *J* = 7.8 Hz, 1H), 7.39 – 7.29 (m, 4H), 7.27 (t, *J* = 6.6 Hz, 1H), 7.12 – 7.02 (m, 3H), 6.88 (d, *J* = 6.9 Hz, 2H), 6.81 (s, 2H), 4.42 (s, 1H), 3.48 (d, *J* = 16.1 Hz, 1H), 3.46 – 3.37 (m, 1H), 2.76 (d, *J* = 16.1 Hz, 1H), 2.32 (s, 6H), 2.17 (s, 3H), 1.55 (d, *J* = 13.1 Hz, 1H), 1.52 – 1.41 (m, 3H), 1.61 – 1.51 (m, 1H), 1.52 – 1.41 (m, 3H), 1.39 – 1.29 (m, 1H), 1.20 – 1.05 (m, 2H), 1.06 – 0.90 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 177.8, 164.2, 138.1, 136.3, 134.6, 134.2, 133.5, 128.4, 128.4, 128.3, 128.0, 127.9, 127.6, 126.2, 54.1, 48.5, 45.8, 32.1, 31.6, 25.2, 24.5, 24.4, 20.6, 19.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{32}H_{37}N_2O_2$ 481.2855; Found 481.2862.

(±)-*trans*-2-Benzyl-3-phenyl-1-(2-phenylacetyl)-*N*-(3,4,5-trimethoxyphenyl)aziridine-2-carboxamide (*rac*-4{44}): Yellow solid, 136 mg, 51% yield, mp 68–69 °C. Silica gel TLC R_f = 0.73 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.13 (s, 1H), 7.48 (d, *J* = 7.7 Hz, 2H), 7.44 (t, *J* = 7.4 Hz, 2H), 7.42 – 7.34 (m, 1H), 7.35 – 7.26 (m, 4H), 7.27 – 7.15 (m, 4H), 7.12 (d, *J* = 7.5 Hz, 2H), 7.07 (s, 2H), 4.02 (s, 1H), 3.75 (s, 6H), 3.62 (s, 3H), 3.60 – 3.49 (m, 2H), 3.30 (s, 9H), 3.20 (d, *J* = 6.7 Hz, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 181.0, 166.3, 152.7, 137.0, 135.4, 134.4, 134.2, 134.0, 129.4, 129.3, 128.6, 128.4, 128.1, 128.0, 127.9, 127.0, 126.4, 98.13, 6.14, 6.52, 55.8, 47.3, 43.2, 32.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{33}H_{33}N_2O_5$ 537.2389; Found 537.2386.

Mixture of ethyl (2*S*, 3*S*)-1-((*S*)-5-(*tert*-butoxy)-4-((*tert*-butoxycarbonyl)amino)-5-oxopentanoyl)-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate and ethyl (2*R*, 3*R*)-1-((*S*)-5-(*tert*-butoxy)-4-((*tert*-butoxycarbonyl)amino)-5-oxopentanoyl)-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (4{45}): amorphous solid, 211 mg, 82% yield. Silica gel TLC R_f = 0.35 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.34, 7.32 (2 x s, 2 x 1 H), 7.12, 7.09 (2 x d, 2 x 1 H, *J* = 8.3 Hz), 4.22 – 4.09 (m, 2 x 2H), 3.88 – 3.70 (m, 2 x 1H), 3.27 (s, 2 x 1H), 2.39 – 2.25 (m, 2 x 1H), 2.23 – 2.08 (m, 2 x 1H), 1.91 – 1.68 (m, 2 x 2H), 1.53, 1.52 (2 x s, 2 x 3H), 1.41 – 1.31 (m, 2 x 18H), 1.29 – 1.24 (m, 2 x 9H), 1.21 (t, *J* = 6.8 Hz, 2 x 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 180.3, 180.2, 171.4, 171.3, 166.4, 166.4, 165.5, 165.5, 155.6, 155.5, 80.4, 80.4, 78.1, 61.4, 53.9, 53.6, 51.7, 51.6, 48.4, 48.4, 42.7, 42.6, 33.4, 33.0, 28.2, 28.2, 27.6, 26.0, 25.9, 4.1, 13.6, 13.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{25}H_{44}N_3O_8$ 514.3128; Found 514.3125.

Mixture of (2*S*, 3*S*)-ethyl *trans*-1-(3-((*tert*-butoxycarbonyl)amino)propanoyl)-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate and (2*R*, 3*R*)-ethyl *trans*-1-(3-((*tert*-butoxycarbonyl)amino)propanoyl)-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{46}): amorphous solid, 287 mg, 70% yield. Silica gel TLC R_f = 0.57 and 0.66 (two diastereomers, hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.55 (s, 1H), 8.54 (s, 1H), 7.88 (d, 2 x 2H, *J* = 7.5 Hz), 7.78 – 7.72 (m, 1H), 7.74 – 7.67 (m, 2 x 2H), 7.49 – 7.42 (m, 1H), 7.40 (t, 2 x 2H, *J* = 7.5 Hz), 7.35 – 7.26 (m, 2 x 2H), 7.27 – 7.20 (m, 13H), 7.20 – 7.13 (m, 17H), 7.12 (s, 1H), 4.36 – 4.27 (m, 2H), 4.27 – 4.18 (m, 4H), 4.17 – 4.01 (m, 6H), 3.19 (s, 1H), 2.36 – 2.13 (m, 4H), 2.05 – 1.88 (m, 4H), 1.74 – 1.62 (m, 2H), 1.50 – 1.44 (m, 6H), 1.24 – 1.19 (m, 18H), 1.19 – 1.12 (m, 6H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.7, 171.4, 166.2, 166.0, 165.5, 165.5, 156.0, 155.8, 145.0, 144.9, 143.9, 143.8, 140.7, 128.6, 127.7, 127.4, 127.1, 126.3, 125.3, 125.3, 120.2, 69.2, 67.3, 65.9, 61.7, 61.3, 55.3, 55.0, 51.6, 46.7, 32.6, 32.4, 28.2, 28.2, 27.5, 22.8, 14.0, 13.3, 13.2. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{50}H_{53}N_4O_7$ 821.3914; Found 821.3905.

(±)-Ethyl *trans*-1-(3-((*tert*-butoxycarbonyl)amino)propanoyl)-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-4{47}): White solid, 150 mg, 75% yield, mp 99–101 °C. Silica gel TLC R_f = 0.57 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35 (s, 1H), 6.66 (t, *J* = 6.0 Hz, 1H), 4.22 – 4.08 (m, 2H), 3.27 (s, 1H), 3.16 – 3.07 (m, 3H), 2.47 – 2.38 (m, 1H), 2.27 – 2.19 (m, 1H), 1.53 (s, 3H), 1.34 (s, 9H), 1.26 (s, 9H), 1.23 – 1.20 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 179.2, 166.4, 165.6, 155.4, 77.6, 61.4, 51.7, 48.4, 42.7, 36.9, 35.9, 28.2, 28.2, 14.1, 13.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{34}N_3O_6$ 400.2448; Found 400.2448.

Mixture of ethyl (2*S*, 3*S*)-1-((*R*)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetyl)-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate and ethyl (2*R*, 3*R*)-1-((*R*)-2-((*tert*-butoxycarbonyl)amino)-2-phenylacetyl)-3-(*tert*-butylcarbamoyl)-3-

methylaziridine-2-carboxylate (4{48}): amorphous solid, 148 mg, 64% yield. Silica gel TLC R_f = 0.81 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (d, J = 9.7 Hz, 1H), 7.41 (d, J = 9.4 Hz, 1H), 7.37 – 7.26 (2 x m, 2 x 5H), 7.24 (s, 1H), 7.19 (s, 1H), 5.23 (d, J = 9.8 Hz, 1H), 5.10 (d, J = 8.7 Hz, 1H), 4.24 – 3.95 (2 x m, 2 x 2H), 3.22 (s, 1H), 3.12 (s, 1H), 1.37 (s, 9H), 1.32 (s, 9H), 1.30 (s, 9H), 1.28 (s, 9H), 1.32 – 1.25 (m, 2 x 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 178.9, 178.9, 166.0, 166.0, 165.7, 165.6, 154.8, 154.7, 138.8, 138.5, 128.3, 128.1, 128.0, 127.7, 127.4, 127.3, 78.5, 78.3, 61.4, 59.8, 58.9, 51.8, 51.7, 49.5, 49.3, 43.0, 42.8, 28.3, 28.2, 28.2, 28.1, 14.0, 13.2, 12.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{24}H_{36}N_3O_6$ 462.2604; Found 462.2608.

General procedure and characterization data for racemic *N*-acylaziridine dicarboxamides 6–11: To a solution of aziridine ester **4** (0.3 mmol, 1 equiv.) in cooled THF (1.5 mL, 0 °C) was added 1 M NaOH solution (0.35 mmol, 1.16 equiv.) dropwise. Then the mixture was warmed up to room temperature and stirred for 12 h. After the ester hydrolysis was completed, the organic solvent was removed under reduced pressure and the resulting residue was used immediately for the next step without any further purification.

To a solution of the above compound in DMF (6 mL) were added *N*-Ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.35 mmol, 1.16 equiv), amine (0.3 mmol, 1 equiv) and 1-Hydroxybenzotriazole (0.41 mmol, 1.38 equiv). The reaction mixture was stirred for 12 h at room temperature, then extracted with EtOAc (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (hexane/Ethyl acetate) to give aziridines **6**–**11**.

(±)-*trans*-1-Benzoyl-N^2-(*tert*-butyl)-N^3-cyclopropyl-2-methylaziridine-2,3-dicarboxamide (*rac*-6): White solid, 76 mg, 74% yield, mp 155–157 °C. Silica gel TLC R_f = 0.33 (toluene/MeCN = 2/1). ^{1}H NMR (500 MHz, $CDCl_3$-d_1) δ 7.79 (d, J = 7.1 Hz, 2H), 7.48 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 7.6 Hz, 2H), 6.53 (s, 1H), 5.73 (s, 1H), 3.70 (s, 1H), 2.83 – 2.69 (m, 1H), 1.65 (s, 3H), 1.01 (s, 9H), 0.87 – 0.74 (m, 2H), 0.65 – 0.44 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$-d_1) δ 175.9, 167.0, 164.2, 133.5, 132.1, 127.9, 127.8, 51.6, 48.6, 45.1, 27.6, 22.0, 14.1, 6.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{26}N_3O_3$ 344.1974; Found 344.1974.

(±)-*trans*-1-Benzoyl-N^2-(*tert*-butyl)-2-methyl-N^3-(prop-2-yn-1-yl)aziridine-2,3-dicarboxamide (*rac*-7): White solid, 87 mg, 85% yield, mp 159–160 °C. Silica gel TLC R_f = 0.45 (toluene/MeCN = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.80 (t, J = 5.7 Hz, 1H), 7.73 (d, J = 7.1 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 7.09 (s, 1H), 3.96 – 3.75 (m, 2H), 3.43 (s, 1H), 3.11 (t, J = 2.5 Hz, 1H), 1.67 (s, 3H), 0.96 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.2, 165.4, 165.1, 133.8, 132.3, 128.4, 127.9, 80.8, 73.0, 51.3, 49.4, 44.2, 28.1, 27.8, 13.5. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{19}H_{24}N_3O_3$ 342.1818; Found 342.1818.

(±)-*trans*-1-Benzoyl-N^2-(*tert*-butyl)-2-methyl-N^3-phenylaziridine-2,3-dicarboxamide (*rac*-8): White solid, 108 mg, 95% yield, mp 188–190 °C. Silica gel TLC R_f = 0.28 (hexane/EtOAc = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.52 (s, 1H), 7.79 (d, J = 7.5 Hz, 2H), 7.65 (d, J = 7.9 Hz, 2H), 7.57 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 7.34 (t, J = 7.9 Hz, 2H), 7.17 (s, 1H), 7.10 (t, J = 7.4 Hz, 1H), 3.71 (s, 1H), 1.77 (s, 3H), 1.02 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.7, 165.7, 164.5, 139.0, 134.3, 132.8, 129.3, 128.9, 128.4, 124.3, 120.0, 51.81, 50.1, 45.2, 28.3, 13.7. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{22}H_{26}N_3O_3$ 380.1974; Found 380.1975.

(±)-*trans*-1-Benzoyl-N^2-cyclohexyl-N^3-cyclopropyl-2-methylaziridine-2,3-dicarboxamide (*rac*-9): White solid, 102 mg, 92% yield, mp 193–195 °C. Silica gel TLC R_f = 0.31 (toluene/MeCN = 2/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.41 (d, J = 3.2 Hz, 1H), 7.74 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 7.3 Hz, 2H), 7.53 (t, J = 7.1 Hz, 1H), 7.44 (t, J = 7.3 Hz, 2H), 3.38 (s, 1H), 3.28 – 3.17 (m, 1H), 2.74 – 2.63 (m, 1H), 1.63 (s, 3H), 1.61 – 1.57 (m, 1H), 1.58 – 1.51 (m, 1H), 1.51 – 1.42 (m, 2H), 1.27 – 0.84 (m, 6H), 0.61 (d, J = 6.1 Hz, 2H), 0.52 – 0.38 (m, 2H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 175.1, 166.4, 165.1, 133.9, 132.2, 128.4, 127.9, 48.9, 44.5, 31.6, 25.1, 24.9, 24.7, 22.5, 13.2, 5.7, 5.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{21}H_{28}N_3O_3$ 370.2131; Found 370.2130.

(±)-*trans*-1-Benzoyl-N^2-(tert-butyl)-N^3-cyclobutyl-2-methylaziridine-2,3-dicarboxamide (*rac*-10): White solid, 81 mg, 68% yield, mp 209–211 °C. Silica gel TLC R_f = 0.46 (toluene/MeCN = 2/1). ^{1}H NMR (500 MHz, $CDCl_3$-d_1) δ 7.83 (d, J = 7.7 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.41 (t, J = 7.6 Hz, 2H), 6.54 (d, J = 7.9 Hz, 1H), 5.80 (d, J = 7.5 Hz, 1H), 4.49 – 4.34 (m, 1H), 3.70 (s, 1H), 3.54 – 3.38 (m, 1H), 2.44 – 2.23 (m, 2H), 2.02 – 1.84 (m, 2H), 1.80 – 1.69 (m, 3H), 1.68 (s, 3H), 1.62 (d, J = 13.3 Hz, 1H), 1.56 – 1.45 (m, 2H), 1.39 – 1.30 (m, 1H), 1.29 – 0.98 (m, 4H), 0.85 – 0.71 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$-d_1) δ 175.6, 164.5, 164.4, 133.4, 132.1, 128.0, 127.8, 48.7, 48.3, 45.3, 44.1, 32.0, 32.0, 30.7,

30.6, 24.9, 24.2, 24.1, 14.7, 13.9. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{20}H_{28}N_3O_3$ 384.2287; Found384.2290.

(±)-*trans*-1-benzoyl-N^3-cyclopropyl-2-methyl-N^2-(2,4,4-trimethylpentan-2-yl)aziridine-2,3-dicarboxamide (*rac*-11): White solid, 104 mg, 87% yield, mp 147–148 °C. Silica gel TLC R_f = 0.56 (toluene/MeCN = 2/1). ^{1}H NMR (500 MHz, $CDCl_3$-d_1) δ 7.80 (d, *J* = 8.0 Hz, 2H), 7.49 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 6.48 (s, 1H), 5.83 (s, 1H), 3.67 (s, 1H), 2.81 – 2.67 (m, 1H), 1.64 (s, 3H), 1.42 (q, *J* = 15.0 Hz, 2H), 1.14 (s, 3H), 1.00 (s, 3H), 0.87 (s, 9H), 0.84 – 0.77 (m, 2H), 0.64 – 0.47 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$-d_1) δ 175.9, 167.0, 163.9, 133.7, 132.1, 128.0, 127.8, 55.7, 52.1, 48.8, 45.0, 31.1, 31.0, 27.7, 27.1, 22.0, 14.1, 6.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{23}H_{34}N_3O_3$ 400.2600; Found 400.2601.

(±)-*trans*-Ethyl 3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate (*rac*-12):[13a] To a solution of ethyl 3-(*tert*-butylcarbamoyl)-3-methyl-1-(2,2,2-trifluoroacetyl)aziridine-2-carboxylate **4**{10} (0.6 mmol, 200 mg) in cooled EtOH (0.8 mL, 0 °C) was added sodium borohydride (0.9 mmol, 35 mg, 1.5 equiv). The mixture was warmed up to room temperature and stirred for 2 h, then quenched with water (10 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The crude material was purified by column chromatography (toluene/MeCN : 8/1) to afford the desired product as white solid (126 mg, 92% yield), mp 60–62 °C. Silica gel TLC R_f = 0.56 (toluene/MeCN = 3/1). ^{1}H NMR (500 MHz, $CDCl_3$-d_1) δ 6.62 (s, 1H), 4.24 (qd, *J* = 7.1, 1.5 Hz, 2H), 2.52 (d, *J* = 8.0 Hz, 1H), 1.52 (s, 3H), 1.38 (s, 1H), 1.31 (d, *J* = 5.3 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$-d_1) δ 169.6, 169.2, 62.0, 50.5, 42.7, 41.3, 28.5, 14.2, 13.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{11}H_{21}N_2O_3$ 229.1552; Found 229.1550.

General procedure and characterization data for racemic oxazolines 13–16:

***Method* A**[26]**:** To a solution of ethyl 1-benzoyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate **4**{1} (*trans*) or **5**{1} (*cis*) (0.5 mmol, 166 mg) in DMF (8 mL) was added sodium iodide (1.25 mmol, 187 mg, 2.5 equiv) and the mixture was stirred for 12 h at 100 °C. Upon completion of the reaction as indicated by TLC, water (10 mL) was added and extracted with EtOAc (2 x 15 mL). The combined extracts were dried over anhydrous Na_2SO_4. The solvents were removed in vacuo, and the residue was purified by column chromatography (hexane/EtOAc: 6/1) to give the corresponding oxazoline **13** and **14**.

(±)-Ethyl *trans*-4-(*tert*-butylcarbamoyl)-4-methyl-2-phenyl-4,5-dihydrooxazole-5-carboxylate (*rac*-13): White solid, 130 mg, 78% yield, mp 91–92 °C. Silica gel TLC R_f = 0.53 (hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ δ 7.93 (d, *J* = 7.8 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 6.72 (s, 1H), 5.40 (s, 1H), 4.25 – 4.11 (m, 2H), 1.35 (s, 3H), 1.26 (s, 9H), 1.24 – 1.18 (m, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 171.6, 168.2, 162.3, 132.5, 128.9, 128.3, 126.2, 81.0, 77.8, 61.3, 50.6, 28.3, 22.0, 14.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_4$ 333.1814; Found 333.1815.

(±)-Ethyl *cis*-4-(*tert*-butylcarbamoyl)-4-methyl-2-phenyl-4,5-dihydrooxazole-5-carboxylate (*rac*-14): Colorless oil, 133 mg, 80% yield. Silica gel TLC R_f = 0.60 (hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 6.71 (s, 1H), 4.92 (s, 1H), 4.13 – 3.98 (m, 2H), 1.50 (s, 3H), 1.23 (s, 9H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.6, 168.6, 162.6, 132.5, 128.9, 128.3, 126.1, 84.2, 78.9, 61.0, 50.3, 28.2, 27.2, 14.0. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_4$ 333.1814; Found 333.1815.

***Method* B**[20]: To a solution of ethyl 1-benzoyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate **4**{1} (*trans*) or **5**{1} (*cis*) (0.5 mmol, 166 mg) in DCM (10 mL) was added boron trifluoride dihydrate (1.5 mmol, 95 μL, 3 equiv) and the mixture was stirred for 6 h at room temperature. Upon completion of the reaction as indicated by TLC, saturated aqueous $NaHCO_3$ (15 mL) was added and extracted with DCM (2 x 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (hexane/EtOAc: 4/1) to give the corresponding oxazoline **15** and **16**.

(±)-Ethyl *trans*-5-(*tert*-butylcarbamoyl)-5-methyl-2-phenyl-4,5-dihydrooxazole-4-carboxylate (*rac*-15): White solid, 141 mg, 85% yield, mp 98–100 °C. Silica gel TLC R_f = 0.38 (hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.25 (s, 1H), 5.05 (s, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 1.48 (s, 3H), 1.25 (s, 9H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 170.7, 169.0, 163.7, 132.3, 128.8, 128.3, 126.6, 87.0, 73.6, 61.0, 50.9, 28.2, 19.6, 14.1. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{25}N_2O_4$ 333.1814; Found 333.1814.

(±)-Ethyl *cis*-5-(*tert*-butylcarbamoyl)-5-methyl-2-phenyl-4,5-dihydrooxazole-4-carboxylate (*rac*-16): Colorless oil, 120 mg, 72% yield. Silica gel TLC R_f = 0.44 (hexane/EtOAc = 3/1). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.00 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.6 Hz, 2H), 7.02 (s, 1H), 4.61 (s, 1H), 4.11 – 4.02 (m, 1H), 4.01 – 3.94 (m, 1H), 1.55 (s, 3H), 1.26 (s, 9H), 1.16 (t, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.5, 169.4, 163.7, 132.3, 128.7, 128.4, 126.6, 88.1, 77.0, 60.8, 50.7, 28.2, 25.6, 13.9. HRMS (ESI) m/z: $[M+H]^+$ Calced for $C_{18}H_{25}N_2O_4$ 333.1814; Found 333.1817.

Ethyl 2-benzamido-4-(*tert*-butylamino)-3-hydroxy-3-methyl-4-oxobutanoate (17): A solution of (±)-ethyl *trans*-1-benzoyl-3-(*tert*-butylcarbamoyl)-3-methylaziridine-2-carboxylate *rac*-**4**{1} (0.3 mmol, 99.7 mg), $Sc(OTf)_3$ (25 mol%, 37 mg) and water (10 equiv., 56 µL) in acetonitrile (1 mL) was stirred for 24 h at room temperature. Then reaction mixture was extracted with water (5 mL) and EtOAc (2 x 5 mL), dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude material was purified by column chromatography (hexane/EtOAc: 4/1) to give product **17** as white solid, 75 mg, 71% yield, mp 141–143 °C. Silica gel TLC R_f = 0.55 (hexane/EtOAc = 1/1). ^{1}H NMR (500 MHz, $CDCl_3$-d_1) δ 7.93 (d, J = 9.5 Hz, 1H), 7.86 (d, J = 7.6 Hz, 2H), 7.53 (t, J = 7.3 Hz, 1H), 7.46 (t, J = 7.5 Hz, 2H), 6.69 (s, 1H), 5.00 (d, J = 9.4 Hz, 1H), 4.96 (s, 1H), 4.29 – 4.14 (m, 2H), 1.47 (s, 3H), 1.34 (s, 9H), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$-d_1) δ 174.7, 172.1, 166.8, 133.2, 131.4, 128.2, 126.8, 75.5, 61.9, 57.8, 50.7, 28.1, 23.8, 13.6. HRMS (ESI) m/z: $[M+H]^+$ Calcd for $C_{18}H_{27}N_2O_5$ 351.1920; Found 351.1922.

Associated content

Supporting Information: ^{1}H NMR and ^{13}C NMR spectra for new compounds, 2D NMR spectra, LC/MS chromatograms.

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