Aziridine-2-carboxaldehyde Dimers Undergo Homo-Ugi 4-Component-5-center Reactions

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Abstract: Dimeric α-aziridine aldehydes have been used as the aldehyde component in Ugi and Passerini reactions. The highly reactive mixed anhydride intermediate is subject to nucleophilic attack by the aziridine, leading to 'homo-Ugi' β-acylaziridinyl-α-aminoamides. The products can be readily transformed into substituted lactones.

Key words: aziridines, aldehydes, multicomponent reactions, heterocycles, amphoteric molecules

Multicomponent reactions (MCRs) with high functional group tolerance are instrumental in efforts to transform simple and readily available starting materials into complex molecules. At first, MCRs were limited to only a few backbones. For example, the Ugi four-component reaction produces the α-acylaminoamide scaffold (Figure 1a).[1] Diversity within the products was realized using building block arrays or by post-condensation modifications.[2] In recent times, a great many variants of MCRs that produce novel scaffolds have been reported.[3]

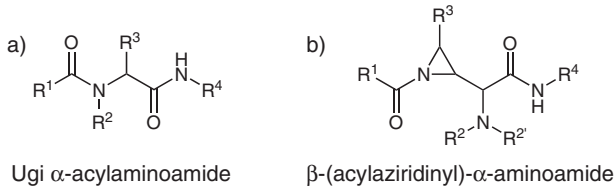

Figure 1 The scaffolds accessible by (a) the original Ugi 4CR, and (b) the modified MCR described herein

Interception of the mixed anhydride intermediates of isocyanide-based multicomponent reactions has led to the development of several new processes. The Ugi–Smiles reaction elaborates heterocycles by substitution of phenols or aromatic thiols for carboxylic acids.[4] Oxazoles synthesized from isocyanoacetates and imines are stable analogues of formylimino anhydrides, and have been transformed in situ using a variety of pericyclic reactions.[5] In the absence of an oxo-component, carboxylic acids have been reacted with isocyanides to produce formimidate carboxylate mixed anhydrides, which function both as strong acylating agents, and are able to rearrange to stable *N*-formyl amides.[6]

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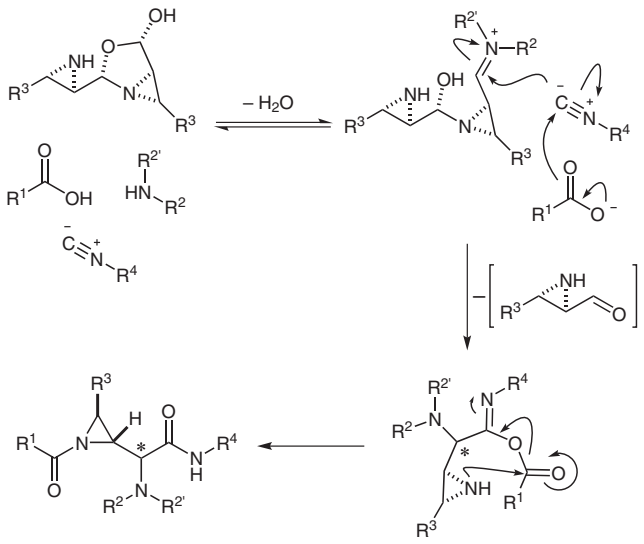
Though aziridines have been synthesized during the course of an Ugi multicomponent reaction,[7] and have been used simultaneously as amine and ketone surrogates in a three component coupling,[8] until recently, no aziridine had been reported to intercept the Ugi reaction. Two years ago, our lab introduced peptide macrocyclization through an intercepted Ugi reaction.[9] Using a reversibly autoprotected aziridine aldehyde as the oxo component, the putative formimino anhydride intermediate is subject to nucleophilic attack from the pendant NH-aziridine. In the case of peptide macrocyclization, this preference for aziridine attack over attack from the secondary amine is explained by the significant ring-strain the latter process would engender. The source of the high diastereoselectivity observed, unusual for Ugi reactions, is likely related to the dimeric and homochiral nature of the aldehyde component. Our lab has observed and reported several examples of aziridine aldehydes disrupting and templating mechanisms of common reactions.[9,10]

Aware that aziridine aldehyde-induced peptide macrocyclization functions through an Ugi-type 3-component 5-centered process, we sought to apply this class of reagents to 4-component-5-centered reactions. We envisioned that the aziridine could intercept the formimino anhydride intermediate to give products based around an unusual β-(acylaziridinyl)-α-aminoamide core (Figure 1b). The 'homo-U-4CR' reaction – which would produce β-(acylamino)amides – has proven elusive.[8,11] With the goal of revealing useful scaffolds derived from aziridine aldehydes, we set out to study intercepted Ugi reactions using untethered carboxylic acid and amine components.

Mechanistically, α-aziridine aldehyde dimers are believed to engage reactants without monomerization.[10b,12] Iminium ion formation is followed by the α-addition of carboxylate to the isocyanide, generating a formimino anhydride (Scheme 1). Aziridine attack on this reactive acylating species leads to the formation of the two amide bonds found in the desired homo-Ugi product. One cannot envision such a process with other secondary amines, since iminium formation would be unselective in those systems. This process is mechanistically similar to aziridine aldehyde induced peptide macrocyclization. Insights into each of these mechanisms could facilitate a deeper understanding of peptide ring-closure kinetics.[13]

In a trial reaction, an equimolar mixture of serine-derived aziridine-2-carboxaldehyde dimer, morpholine, *tert*-butyl isocyanide, and 4-hydroxyphenylacetic acid were mixed



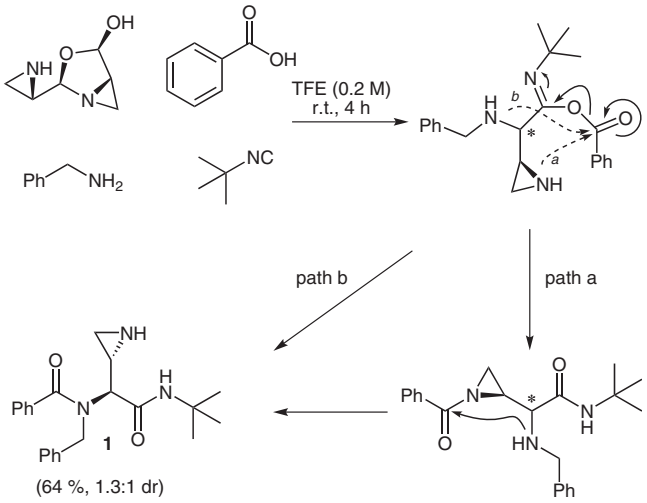
Scheme 1 Proposed mechanism of 'intercepted Ugi' reaction

in 2,2,2-trifluoroethanol (TFE) at room temperature. The desired intercepted-Ugi product was formed in 70% yield (*anti*/*syn* = 1.15:1). By conducting the reaction in different classes of solvents it was found that the process would also take place in water, dichloromethane, *N*,*N*-dimethylformamide, or methanol. Toluene did not facilitate the reaction, presumably due to poor solubility of the carboxylic acid. While the isolated yields from each suitable reaction solvent were comparable, product formation was fastest in TFE. Addition of excess components did not influence the reaction efficiency. The reaction appears to reach completion within four hours. The optimal order of addition was combination of the aldehyde and amine, followed by sequential addition of the isocyanide and acid components.

The intercepted Ugi reaction was then tested with a variety of differentially functionalized inputs (Table 1). Yields ranged from moderate to excellent, while diastereoselectivity was modest in most cases. Aromatic and aliphatic carboxylic acids were well tolerated. Heterocycles, phenols, nitro groups, aryl halides, and even an aniline did not interfere with the reaction course. A variety of isocyanides were tested, and all were compatible with the reaction. Of particular note are the fluorescent isocyanide[14] (entry 5) and thioester isocyanides[15] (entries 6 and 16). As well, both substituted and unsubstituted aziridine aldehydes performed similarly under these conditions.

Save for a few examples with poor selectivity, in each case the *anti*-isomer was preferred. This was established by comparison of $^{3}J_{H,H}$ coupling constants of the newly formed stereocenter. Previous studies have found that the carboxylate directly facilitates isocyanide addition to iminium ions.[16] In peptide macrocyclization, the high facial selectivity of isocyanide addition can be rationalized by the presence of a tethered carboxylate, which could predispose the imine toward selective attack. In the present reaction, there is less preorganization involved in iminium activation.

Cyclic secondary amines such as morpholine and pyrrolidine afforded the best yields due to increased rate of iminium ion formation. Dibenzylamine also performed well in the reaction, but aliphatic secondary amines, such as diethylamine, were not tolerated. This mirrors our findings in peptide macrocyclization, where a proline-terminated peptide is the ideal amine component. When isopropylamine was used, a complex mixture was formed, from which no desired product could be isolated. Benzylamine, however, did participate in the reaction (Scheme 2). Interestingly, isolation and characterization revealed that the aziridine amide was not present in the product **1**. Rather, the product of an uninterrupted Ugi reaction was formed. This stands in contrast to the analogous reaction with primary amino acids, which give stable cyclic products that contain both the activated aziridine amide and a secondary amine.[9] In those cases, aziridine attack on the formimido anhydride intermediate is kinetically favored. These observations have been attributed both to the high nucleophilicity of NH-aziridines, as well to ring strain preventing amine attack. It is not currently known whether the aziridine amide is an intermediate in the present reaction.

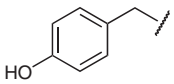
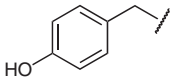
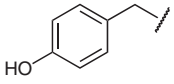
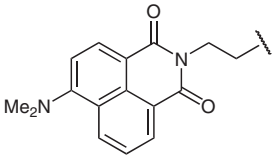
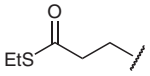
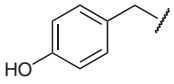
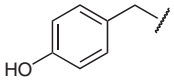
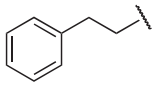
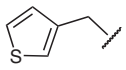
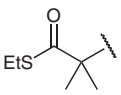
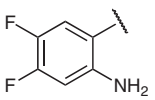


Scheme 2 Reaction of aziridine-2-carboxaldehyde, benzoic acid, benzylamine, and *tert*-butyl isocyanide, and possible mechanistic pathways

In a few cases when using aliphatic carboxylic acids, minor products were observed after flash chromatography. These products were characterized as lactones **2** and **3**, and are believed to form via intramolecular amide O-attack on the activated aziridine (Scheme 3). The relative stereochemistry of **2** was established using ^{1}H NMR coupling constant analysis and 2D NMR spectra. The structure of this compound was confirmed unambiguously by X-ray crystallography (Scheme 3). We screened Lewis acids to initiate this rearrangement in solution, but were fruitless in this search. Heating the aziridine amide in dichloromethane in the presence of silica gel, however, did

afford the desired lactone in synthetically useful yield. *N*-Acylaziridines are typically subject to rearrangement to oxazolines in the presence of acid.[17] In our case, however, attack from the auxiliary *tert*-butylamide is faster. Ring substitution is followed by imidate hydrolysis to construct the observed lactones. This unanticipated transformation demonstrates the value of exploration into novel molecular scaffolds, as well as the bountiful reactivity accessible from aziridine aldehydes.

Table 1 Intercepted Ugi Reactions with Aziridine Aldehyde Dimers[a]

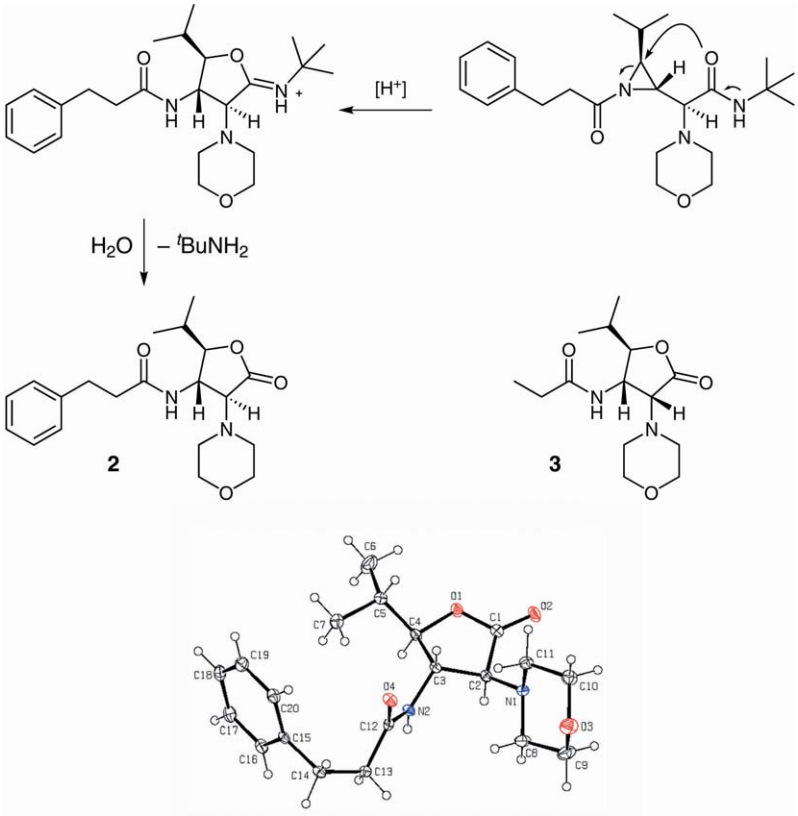
Entry	R^1	R^2, $R^{2'}$	R^3 (*R*/*S*)[b]	R^4	Yield (%)[c]	*anti*/*syn* dr[d]
1		-$CH_2CH_2OCH_2CH_2$-	H (-,*S*)	*t*-Bu	70	1.2:1
2		-$CH_2(CH_2)_2CH_2$-	H (-,*S*)	*t*-Bu	80	2:1
3		Bn, Bn	H (-,*S*)	*t*-Bu	89	3:1
4	3-pyridyl	Et, Et	H (-,*S*)	*t*-Bu	0	n/a
5	3-pyridyl	-$CH_2(CH_2)_2CH_2$-	H (-,*S*)		91	3:1
6	Ph	-$CH_2CH_2OCH_2CH_2$-	H (-,*S*)		72	3.5:1
7	Et	-$CH_2CH_2CHPhCH_2CH_2$-	H (-,*S*)	*t*-Bu	80	1.2:1
8	4-$(NO_2)C_6H_4$	-$CH_2CH_2OCH_2CH_2$-	H (-,*S*)	*t*-Bu	94	1:1
9		-$CH_2(CH_2)_2CH_2$-	*i*-Pr (*S*,*R*)	*t*-Bu	85	2.6:1
10		-$CH_2(CH_2)_2CH_2$-	Me (*S*,*R*)	*t*-Bu	79	3.6:1
11		-$CH_2CH_2OCH_2CH_2$-	*i*-Pr (*S*,*R*)	*t*-Bu	83	0.6:1
12	Ph	-$CH_2(CH_2)_2CH_2$-	*i*-Pr (*S*,*R*)	*t*-Bu	63	1.1:1
13	Et	-$CH_2CH_2OCH_2CH_2$-	*i*-Pr (*S*,*R*)	*t*-Bu	81	4:1
14	3-pyridyl	Bn, Bn	*i*-Pr (*S*,*R*)	*t*-Bu	90	1.8:1
15		-$CH_2(CH_2)_2CH_2$-	*i*-Pr (*S*,*R*)	*t*-Bu	82	0.9:1
16	2-BrC_6H_4	-$CH_2(CH_2)_2CH_2$-	*i*-Pr (*S*,*R*)		59	1.1:1
17		-$CH_2CH_2OCH_2CH_2$-	*i*-Pr (*S*,*R*)	*t*-Bu	72	3:1

[a] Reaction conditions: acid (0.1 mmol), amine (0.1 mmol), aziridine aldehyde dimer (0.05 mmol), isocyanide (0.1 mmol), TFE (0.2 M), 23 °C, 4 h

[b] Assignments refer to: (R^3 substituent position, α-aldehyde position).

[c] Determined by recovery of starting material (b.r.s.m.).

[d] Determined by inspection of crude ^{1}H NMR analysis.



Scheme 3 Lactones synthesized by aziridine ring opening on silica gel and crystal structure of **2**

Finally, another surprising observation was made during the course of these studies. The Ugi reaction is often chemoselective due to the reversibility of the elementary steps leading up to isocyanide attack on an activated iminium ion. Indeed, the barrier to isocyanide attack is great enough that recent studies suggest the requirement for general acid activation of the imine prior to isocyanide attack.[16] This also explains why Passerini products are seldom observed during Ugi reactions. Surprisingly, the formation of Passerini products was observed during a few of our reactions. When we replicated these examples in the absence of amine, we were further surprised that the intercepted Passerini products were formed rapidly, nearly at a comparable rate to the Ugi products (Figure 2). In the course of our investigations into peptide macrocyclization, we have been trying to explain the high rate of reactivity of aziridine aldehyde-induced macrocyclization. This result seems to suggest that an aziridine aldehyde is similarly susceptible to isocyanide attack as an aziridine imine may be, and parallels some of our findings in reductive amination.[10a] In addition, the Passerini β-(acylaziridinyl)-α-hydroxyamides contain a core scaffold entirely unreported in the literature.

In summary, we have reported an application of unprotected aziridine aldehyde dimers in isocyanide-based multicomponent reactions. The Ugi and Passerini reactions are disrupted from their normal course by the presence of a pendant aziridine. The products formed are unrepresented in the literature, and display rich and potentially useful reactivity. This study has also produced findings that will help to reveal the nature of aziridine aldehyde reactivity, including macrocyclization applications.

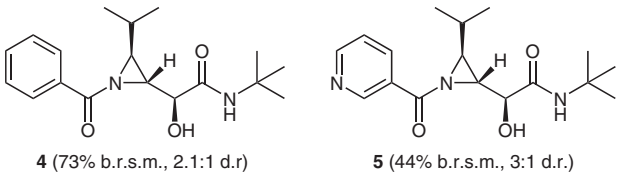


Figure 2 Products of intercepted Passerini reaction

All reactions were carried out under an atmosphere of air unless otherwise stated. Reagents were used as obtained from commercial suppliers or purified according to standard procedures. Aziridine-2-carboxaldehyde was synthesized according to literature procedure.[9b] THF was distilled from sodium benzophenone ketyl under N_2. TFE and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) were purchased from Oakwood Products (West Columbia, SC). Anhyd toluene and Et_2O were obtained using the method described by Grubbs.[18] Flash chromatography was performed using SiliaFlash P60 40–63 μm silica gel. TLC was performed on EMD silica gel 60 F_{254} TLC glass plates and visualized with UV light, and I_2 on silica or permanganate stain. All ^1H and ^{13}C NMR spectra were recorded using a Bruker 400 MHz and Varian 200, 300 or 400 MHz spectrometers and were internally referenced to residual protiosolvent. 2D (COSY, HSQC) NMR spectroscopy was used where appropriate to assist the assignment of signals in the ^1H and ^{13}C NMR spectra. LC-MS (ESI) was recorded on an Agilent 1200 Series quadrupole spectrometer.

(*S*)-Boc-Valinol

Boc-valine (50 g, 0.23 mol) was loaded into a round-bottomed flask. THF (230 mL) was added, and the resulting solution was cooled to –10 °C. *i*-Pr_2EtN (40 mL, 0.23 mol) was added, followed by isobutyl chloroformate (30 mL, 0.23 mol). The mixture was stirred for 15 min and vacuum filtered into a 500 mL round-bottomed flask. The filtrate was cooled to –10 °C. $NaBH_4$ (13.05 g, 0.345 mmol) was dissolved in H_2O (108 mL) and added using an addition funnel over 5 min (**CAUTION**: Gas evolution! Rapid addition will lead to product loss.) After the addition is complete, the reaction is diluted with H_2O (100 mL) and extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated to yield the title compound; yield: 45.1 g (96%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (d, *J* = 7.9 Hz, 1 H), 3.63 (ddd, *J* = 17.4, 11.1, 4.9 Hz, 2 H), 3.39 (d, *J* = 6.5 Hz, 1 H), 1.89–1.69 (m, 1 H), 1.43 (s, 9 H), 0.97–0.87 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.3, 157.0, 79.6, 69.8, 64.2, 60.5, 58.2, 28.5, 19.6, 19.0, 18.6, 14.3.

(*S*)-Boc-Alaninol

The title compound was prepared in an analogous method to the isopropyl derivative described above; yield: 12.9 g (70%); colorless oil.

^{1}H NMR (399 MHz, $CDCl_3$): δ = 4.73 (s, 1 H), 3.73 (d, *J* = 4.2 Hz, 1 H), 3.60 (dd, *J* = 11.0, 3.9 Hz, 1 H), 3.48 (dd, *J* = 11.0, 6.1 Hz, 1 H), 3.38 (d, *J* = 6.5 Hz, 1 H), 1.42 (s, 9 H), 1.12 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5, 69.8, 30.9, 28.5, 19.0.

(*S*)-*tert*-Butyl 2-Isopropylaziridine-1-carboxylate[19]

Boc-valinol (15.2 g, 75 mmol) and TsCl (17.2 g, 90 mmol) were dissolved in anhyd Et_2O (1.5 L). Fresh, finely powdered KOH (16.8 g, 300 mmol) was added to the flask. (Important: KOH pellets, not flakes, should be used.) The mixture was heated to reflux until completion, as detected by TLC (~16 h). The mixture was then poured into a separatory funnel containing ice and H_2O. The organic layer was separated, washed with brine (250 mL), dried ($MgSO_4$), filtered, and concentrated. The title compound was isolated by vacuum distillation (42 °C/2 Torr); yield: 7.2 g (52%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (d, *J* = 6.2 Hz, 1 H), 2.12 (ddd, *J* = 7.4, 6.2, 3.9 Hz, 1 H), 1.93 (d, *J* = 3.8 Hz, 1 H), 1.44 (s, 9 H), 1.39 (dd, *J* = 13.7, 6.9 Hz, 1 H), 1.05 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.0, 80.9, 44.5, 31.1, 30.8, 28.0, 19.9, 19.2.

(*S*)-*tert*-Butyl 2-Methylaziridine-1-carboxylate[19]

The title compound was prepared in an analogous method to the isopropyl derivative described above. Vacuum distillation: 30 °C/5 Torr; yield: 6.9 g (59%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.48–2.39 (m, 1 H), 2.23 (d, *J* = 5.9 Hz, 1 H), 1.87 (d, *J* = 3.8 Hz, 1 H), 1.45 (s, 9 H), 1.26 (d, *J* = 5.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.6, 81.0, 69.9, 33.7, 32.6, 28.1, 19.0, 17.5.

(2*R*,3*S*)-*tert*-Butyl 3-Isopropylaziridine-2-carboxylate[20]

A flame-dried flask with a stir bar was cooled to r.t. under N_2. THF (76 mL) and 2,2,6,6-tetramethylpiperidine (188 mL, 75.3 mmol) were added by syringe. The contents were cooled to –78 °C. *n*-BuLi (1.6 M in hexanes, 47.1 mL, 75.3 mmol) was added dropwise to the flask by cannulation. The flask was then warmed at r.t. for 30 min, then cooled again to –78 °C. (*S*)-*tert*-Butyl 2-isopropylaziridine-1-carboxylate (4.65 g, 25.1 mmol) was dissolved in THF (76 mL), and added to the flask by cannulation over 30 min. The reaction mixture was stirred at –78 °C for 2 h or until completion. Sat. aq NH_4Cl (100 mL) was added slowly to the flask, which was then warmed to r.t. The product was extracted with EtOAc (3 × 100 mL), and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. The product was purified by vacuum distillation (47 °C/5 Torr); yield: 3.55 g (76%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.22 (dd, *J* = 7.3, 2.5 Hz, 1 H), 1.94 (ddd, *J* = 10.0, 7.6, 2.5 Hz, 1 H), 1.47 (s, 9 H), 1.31 (dd, *J* = 13.9, 7.0 Hz, 1 H), 0.99 (dd, *J* = 18.5, 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 81.9, 45.7, 35.4, 31.4, 28.2, 20.1, 19.7.

(2*R*,3*S*)-*tert*-Butyl 3-Methylaziridine-2-carboxylate[20]

The title compound was prepared in an analogous method to the isopropyl derivative described above; yield: 0.8 g (20%); pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.23–2.16 (m, 1 H), 2.16–2.12 (m, 1 H), 1.47 (s, 9 H), 1.21 (d, *J* = 5.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.0, 82.0, 37.2, 34.4, 28.2, 18.2.

(2*S*,4*S*,5*R*,6*S*)-6-Isopropyl-2-[(2*R*,3*S*)-3-isopropylaziridin-2-yl]-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol

To a flame-dried Schlenk flask equipped with a stir bar and a rubber septum under N_2 was cannulated (2*R*,3*S*)-*tert*-butyl 3-isopropylaziridine-2-carboxylate (1.5 g, 8.1 mmol, 1.0 equiv) in toluene (27 mL). The flask was cooled to –78 °C with stirring before DIBAL-H (1.0 M, 16.2 mL, 16.2 mmol, 2.0 equiv) was added over 20 min by cannulation. After 2 h, the reaction was judged to be complete by TLC (eluent: 25% EtOAc–hexanes), and MeOH (0.51 mL, 12.2 mmol, 1.5 equiv) was added over 10 min. The flask was warmed to r.t., after which sat. aq Na_2SO_4 (2 mL) was added to induce precipitation of aluminum salts. The salts were removed by filtration and washing with EtOAc (15 mL). The filtrate was diluted with H_2O (15 mL), and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The product was purified by flash chromatography (EtOAc–1% Et_3N–MeOH, 9:1); yield: 545 mg (60%); colorless solid; R_f = 0.14 (EtOAc–MeOH, 9:1).

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.25 (s, 1 H), 4.90 (s, 1 H), 2.46 (d, *J* = 2.9 Hz, 1 H), 2.19 (br s, 1 H), 1.84 (br s, 1 H), 1.28 (m, 3 H), 1.16 (dd, *J* = 8.2, 2.9 Hz, 1 H), 1.03–0.98 (m, 12 H), 0.94 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 96.6, 94.8, 49.9, 45.9, 40.6, 37.6, 32.3, 30.4, 20.3, 20.3, 20.2, 19.8.

MS (ESI): *m*/*z* = 227.2 [M + H].

(2*S*,4*S*,5*R*,6*S*)-6-Methyl-2-[(2*R*,3*S*)-3-methylaziridin-2-yl]-3-oxa-1-azabicyclo[3.1.0]hexan-4-ol

The title compound was prepared in an analogous method to the isopropyl derivative described above; yield: 205 mg (48%); pale yellow semi-solid; R_f < 0.1 (EtOAc–MeOH, 9:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.24 (s, 1 H), 4.94 (s, 1 H), 2.39 (d, *J* = 2.9 Hz, 1 H), 2.12 (d, *J* = 2.6 Hz, 1 H), 2.07–1.95 (m, 1 H), 1.51–1.42 (m, 1 H), 1.29 (d, *J* = 5.6 Hz, 3 H), 1.17 (d, *J* = 5.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.4, 94.2, 51.3, 39.7, 34.3, 29.6, 18.7, 16.5.

MS (ESI): *m*/*z* = 171.1 [M + H].

Multicomponent Reactions; General Procedure

A solution of aziridine aldehyde dimer (0.05 mmol, 0.5 equiv) and amine (0.1 mmol, 1.0 equiv) in TFE (to make a 0.4 M solution of the dimer) was mixed at r.t. for 5 min. Sequentially, isocyanide (0.1 mmol, 1.0 equiv) and carboxylic acid (0.1 mmol, 1.0 equiv) were added. The reaction mixture was then stirred for 4 h, monitoring by TLC (eluent: 50% EtOAc–hexanes) and LCMS. The reaction mixture was then diluted with CH_2Cl_2 (10 mL) and washed with H_2O (4 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). If

an emulsion formed, this was broken up by addition of brine. The combined organic layers were dried (Na_2SO_4), filtered and concentrated. The crude residue was purified by flash chromatography using hexanes and EtOAc.

(*S*)-*N*-(*tert*-Butyl)-2-{(*S*)-1-[2-(4-hydroxyphenyl)acetyl]aziridin-2-yl}-2-morpholinoacetamide (Table 1, entry 1)
Yield: 70 mg (70%); dr = 1.2:1; yellow semi-solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (br s, 1 H), 7.08 (d, *J* = 8.5 Hz, 2 H), 6.76 (d, *J* = 8.5 Hz, 2 H), 3.73–3.67 (m, 4 H), 3.64 (d, *J* = 6.2 Hz, 2 H), 2.94–2.83 (m, 2 H), 2.61 (ddd, *J* = 11.2, 7.0, 3.8 Hz, 3 H), 2.35 (d, *J* = 8.8 Hz, 1 H), 2.32 (d, *J* = 3.1 Hz, 1 H), 2.20 (d, *J* = 6.4 Hz, 1 H), 1.34 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.2, 169.6, 155.8, 130.6, 125.4, 115.7, 73.3, 67.3, 51.1, 43.2, 35.5, 29.4, 28.8, 19.2.

MS (ESI): *m*/*z* = 376.5 [M + H].

(*S*)-*N*-(*tert*-Butyl)-2-{(*S*)-1-[2-(4-hydroxyphenyl)acetyl]aziridin-2-yl}-2-(pyrrolidin-1-yl)acetamide (Table 1, entry 2)
Yield: 100.6 mg (80%); dr = 2:1; colorless wax.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.08 (d, *J* = 8.5 Hz, 2 H), 7.01 (s, 1 H), 6.78 – 6.73 (d, *J* = 8.5 Hz, 2 H), 3.64 (d, *J* = 3.6 Hz, 2 H), 2.83 (dd, *J* = 6.9, 2.4 Hz, 2 H), 2.73–2.64 (m, 3 H), 2.36 (d, *J* = 8.6 Hz, 1 H), 2.33 (d, *J* = 3.2 Hz, 1 H), 2.15 (d, *J* = 6.5 Hz, 1 H), 2.04 (s, 1 H), 1.77 (s, 4 H), 1.34 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.0, 170.0, 155.5, 130.6, 125.8, 115.7, 72.2, 51.5, 51.0, 43.3, 37.2, 29.1, 28.8, 23.5.

MS (ESI): *m*/*z* = 360.3 [M + H].

(*S*)-*N*-(*tert*-Butyl)-2-(dibenzylamino)-2-{(*S*)-1-[2-(4-hydroxyphenyl)acetyl]aziridin-2-yl}acetamide (Table 1, entry 3)
Yield: 22.5 mg (89%); dr = 3:1; colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36 (s, 1 H), 7.33–7.24 (m, 10 H), 7.13 (d, *J* = 8.5 Hz, 2 H), 6.79 (d, *J* = 8.5 Hz, 2 H), 3.98 (d, *J* = 13.3 Hz, 2 H), 3.86–3.79 (m, 3 H), 3.70 (d, *J* = 6.3 Hz, 2 H), 2.97–2.90 (m, 1 H), 2.82 (d, *J* = 8.8 Hz, 1 H), 2.38 (d, *J* = 6.4 Hz, 1 H), 2.13 (d, *J* = 3.0 Hz, 1 H), 1.32 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.8, 170.5, 155.7, 138.9, 130.5, 129.0, 128.6, 128.6, 128.4, 127.4, 127.2, 125.9, 115.8, 63.9, 54.4, 53.2, 51.1, 43.5, 33.1, 29.9, 28.8.

MS (ESI): *m*/*z* = 486.7 [M + H].

***N*-{2-[6-(Dimethylamino)-1,3-dioxo-1*H*-benzo[*de*]isoquinolin-2(3*H*)-yl]ethyl}-2-(1-nicotinoylaziridin-2-yl)-2-(pyrrolidin-1-yl)acetamide (Table 1, entry 5)**
Yield: 39 mg (91%); dr = 3:1; orange solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.08 (d, *J* = 1.4 Hz, 1 H), 8.64 (dd, *J* = 4.9, 1.6 Hz, 1 H), 8.46 (dd, *J* = 7.3, 1.1 Hz, 1 H), 8.35 (d, *J* = 8.2 Hz, 1 H), 8.27 (dd, *J* = 8.5, 1.1 Hz, 1 H), 8.16 (d, *J* = 8.0 Hz, 1 H), 7.53 (dd, *J* = 8.5, 7.3 Hz, 1 H), 7.25 (dd, *J* = 7.7, 5.1 Hz, 1 H), 6.97 (d, *J* = 8.3 Hz, 1 H), 4.40–4.32 (m, 1 H), 3.73–3.67 (m, 2 H), 3.61–3.54 (m, 2 H), 3.05 (s, 3 H), 2.99 (s, 3 H), 2.86 (m, 4 H), 2.77 (d, *J* = 8.7 Hz, 1 H), 2.55 (d, *J* = 3.3 Hz, 1 H), 2.14 (d, *J* = 6.6 Hz, 1 H), 1.81 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.6, 176.7, 170.9, 170.0, 133.3, 133.1, 133.1, 132.3, 130.1, 130.1, 130.0, 129.2, 129.1, 128.6, 128.5, 128.5, 128.4, 128.3, 127.1, 72.9, 67.1, 50.7, 43.2, 35.2, 35.0, 34.2, 23.4, 14.7.

MS (ESI): *m*/*z* = 541.8 [M + 1].

***S*-Ethyl 3-{(*S*)-2-[(*S*)-1-Benzoylaziridin-2-yl]-2-morpholinoacetamido}propanethioate (Table 1, entry 6)**
Yield: 54.1 mg (72%); dr = 3.2:1; pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03 (dd, *J* = 5.1, 3.3 Hz, 2 H), 7.63 (t, *J* = 6.0 Hz, 1 H), 7.54 (ddd, *J* = 6.9, 4.0, 1.2 Hz, 1 H), 7.44 (t, *J* = 7.6 Hz, 2 H), 3.74 (dt, *J* = 5.7, 3.7 Hz, 4 H), 3.58 (dd, *J* = 9.8, 6.0 Hz, 2 H), 3.01–2.92 (br m, 3 H), 2.89 (dd, *J* = 14.8, 7.4 Hz, 2 H), 2.79 (t, *J* = 5.9 Hz, 2 H), 2.69–2.58 (m, 4 H), 2.36 (d, *J* = 6.6 Hz, 1 H), 1.24 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.4, 178.7, 170.5, 133.2, 132.4, 129.2, 128.6, 73.0, 67.2, 51.3, 43.3, 35.2, 35.2, 31.7, 23.5, 14.8.

MS (ESI): *m*/*z* = 406.2 [M + 1].

(*S*)-*N*-(*tert*-Butyl)-2-(4-phenylpiperidin-1-yl)-2-[(*S*)-1-propionylaziridin-2-yl]acetamide (Table 1, entry 7)
Yield: 18.6 mg (80%); dr = 1.2:1; pale solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.28 (m, 2 H), 7.22 (dd, *J* = 7.8, 2.9 Hz, 3 H), 6.64 (s, 1 H), 4.96 (dd, *J* = 12.5, 6.2 Hz, 1 H), 4.86 (ddd, *J* = 10.4, 8.1, 4.4 Hz, 1 H), 4.02 (dd, *J* = 14.3, 8.1 Hz, 1 H), 3.94–3.85 (m, 1 H), 3.10 (d, *J* = 11.3 Hz, 1 H), 2.90 (d, *J* = 4.4 Hz, 1 H), 2.44 (ddd, *J* = 9.6, 7.9, 5.4 Hz, 2 H), 2.31 (d, *J* = 7.6 Hz, 1 H), 2.29–2.23 (m, 2 H), 1.95–1.82 (m, 2 H), 1.80–1.62 (m, 2 H), 1.37 (d, *J* = 3.8 Hz, 3 H), 1.35 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.1, 168.6, 146.0, 128.6, 126.9, 126.4, 76.3, 72.3, 57.4, 52.8, 50.6, 42.4, 34.0, 28.9, 22.1, 21.7.

MS (ESI): *m*/*z* = 372.7 [M + 1].

(*S*)-*N*-(*tert*-Butyl)-2-morpholino-2-[(*S*)-1-(4-nitrobenzoyl)aziridin-2-yl]acetamide (Table 1, entry 8)
Yield: 12.2 mg (94%); dr = 1:1; yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (tt, *J* = 12.7, 7.7 Hz, 4 H), 6.50 (s, 1 H), 5.02–4.93 (m, 2 H), 3.79–3.74 (m, 2 H), 3.01–2.92 (m, 1 H), 2.71 (d, *J* = 3.4 Hz, 1 H), 2.61 (d, *J* = 8.9 Hz, 1 H), 2.43 (d, *J* = 6.5 Hz, 1 H), 1.25 (s, 9 H).

MS (ESI): *m*/*z* = 391.2 [M + 1].

(*R*)-*N*-(*tert*-Butyl)-2-{(2*R*,3*S*)-1-[2-(4-hydroxyphenyl)acetyl]-3-isopropylaziridin-2-yl}-2-(pyrrolidin-1-yl)acetamide (Table 1, entry 9)
Yield: 26 mg (94%); dr = 1:1; colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.37 (s, 1 H), 7.12 (d, *J* = 8.5 Hz, 2 H), 6.85 (s, 1 H), 6.76 (d, *J* = 8.6 Hz, 2 H), 3.64 (dd, *J* = 51.7, 15.6 Hz, 2 H), 2.73 (dd, *J* = 6.9, 3.2 Hz, 4 H), 2.67 (m, 1 H), 2.51 (dd, *J* = 8.1, 3.2 Hz, 1 H), 2.33 (d, *J* = 7.9 Hz, 1 H), 1.73 (t, *J* = 2.9 Hz, 4 H), 1.58–1.49 (m, 1 H), 1.35 (s, 9 H), 1.16 (d, *J* = 6.7 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.9, 170.5, 154.9, 130.7, 126.8, 115.6, 72.2, 51.7, 50.8, 48.5, 44.0, 41.7, 29.8, 28.9, 23.6, 21.6, 19.8.

MS (ESI): *m*/*z* = 402.7 [M + 1].

***N*-(*tert*-Butyl)-2-{1-[2-(4-hydroxyphenyl)acetyl]-3-methylaziridin-2-yl}-2-(pyrrolidin-1-yl)acetamide (Table 1, entry 10)**
Yield: 34 mg (85%); dr = 2.6:1; pale oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (dd, *J* = 8.0, 6.4 Hz, 2 H), 7.24–7.20 (m, 2 H), 6.76 (s, 1 H), 3.45 (s, 1 H), 3.27 (dd, *J* = 3.7, 1.8 Hz, 1 H), 3.23 (d, *J* = 3.5 Hz, 1 H), 2.53 (dd, *J* = 14.4, 10.4 Hz, 1 H), 2.23 (ddd, *J* = 6.8, 5.8, 3.6 Hz, 1 H), 1.86 (dd, *J* = 13.6, 6.8 Hz, 2 H), 1.77 (s, 2 H), 1.56 (dt, *J* = 13.2, 5.3 Hz, 2 H), 1.44 (dd, *J* = 7.6, 5.9 Hz, 2 H), 1.03 (s, 9 H), 1.01 (dd, *J* = 6.7, 3.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.6, 172.0, 150.1, 130.1, 126.4, 118.9, 57.3, 53.2, 43.4, 41.0, 40.5, 35.1, 28.5, 26.6, 22.4.

MS (ESI): *m*/*z* = 374.1 [M + 1].

(*R*)-*N*-(*tert*-Butyl)-2-[(2*R*,3*S*)-3-isopropyl-1-(3-phenylpropanoyl)aziridin-2-yl]-2-morpholinoacetamide (Table 1, entry 11)
Yield: 31 mg (79%); dr = 3.6:1; crystalline colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 3.5 Hz, 2 H), 7.20 (dd, *J* = 7.5, 2.7 Hz, 2 H), 6.37 (s, 1 H), 4.43 (dd, *J* = 6.6, 4.4 Hz, 1 H), 4.06 (t, *J* = 6.1 Hz, 1 H), 3.71 (t, *J* = 4.5 Hz, 4 H), 3.65–3.57 (m, 1 H), 2.94 (dd, *J* = 12.2, 4.9 Hz, 2 H), 2.66–2.51 (m, 6 H), 1.75–1.65 (m, 1 H), 1.34–1.31 (m, 9 H), 0.88 (dd, *J* = 10.8, 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 179.2, 167.7, 165.1, 140.8, 128.6, 128.5, 126.3, 74.1, 73.2, 67.3, 51.3, 51.1, 32.7, 32.4, 30.0, 28.9, 18.5, 18.3.

MS (ESI): *m*/*z* = 416.6 [M + 1].

2-[(2*R*,3*S*)-1-Benzoyl-3-isopropylaziridin-2-yl]-*N*-(*tert*-butyl)-2-(pyrrolidin-1-yl)acetamide (Table 1, entry 12)
Yield: 12.4 mg (83%); dr = 1.6:1; colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ (major isomer) = 8.06–8.01 (m, 2 H), 7.42 (ddd, *J* = 12.6, 5.6, 2.0 Hz, 3 H), 6.96 (s, 1 H), 4.61 (dd, *J* = 6.4, 3.0 Hz, 1 H), 4.28 (t, *J* = 6.2 Hz, 1 H), 2.70–2.62 (m, 4 H), 2.35 (dd, *J* = 13.2, 5.7 Hz, 1 H), 1.79–1.72 (m, 4 H), 1.37 (s, 9 H), 1.25 (d, *J* = 6.8 Hz, 1 H), 0.80 (d, *J* = 6.8 Hz, 3 H), 0.63 (d, *J* = 6.6 Hz, 3 H); δ (minor isomer) = 7.98 (dd, *J* = 8.3, 1.3 Hz, 2 H), 7.53 (dd, *J* = 4.9, 3.6 Hz, 2 H), 6.45 (s, 1 H), 3.95 (t, *J* = 5.2 Hz, 1 H), 3.65 (t, *J* = 7.0 Hz, 1 H), 3.42 (t, *J* = 6.6 Hz, 1 H), 2.84–2.80 (m, 4 H), 1.83 (t, *J* = 6.3 Hz, 4 H), 1.17 (s, 1 H), 1.08 (s, 9 H), 1.02–0.99 (m, 3 H), 0.94 (dd, *J* = 6.8, 2.7 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ (both isomers) = 178.1, 170.2, 168.4, 162.0, 134.9, 132.9, 131.3, 130.0, 129.4, 128.5, 128.4, 128.4, 80.5, 74.5, 73.7, 73.6, 52.0, 51.8, 51.6, 50.8, 50.6, 41.0, 33.0, 29.5, 28.9, 28.4, 23.6, 23.5, 21.0, 20.4, 18.6, 18.2.

MS (ESI): *m*/*z* = 372.3 [M + 1].

(*R*)-*N*-(*tert*-Butyl)-2-[(2*R*,3*S*)-3-isopropyl-1-propionylaziridin-2-yl]-2-morpholinoacetamide (Table 1, entry 13)
Yield: 9.6 mg (63%); dr = 1.1:1; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.44 (s, 1 H), 4.43 (dd, *J* = 6.6, 4.2 Hz, 1 H), 4.06 (t, *J* = 6.2 Hz, 1 H), 3.73 (dd, *J* = 6.5, 2.7 Hz, 3 H), 2.70–2.56 (m, 5 H), 2.26 (qd, *J* = 7.6, 1.1 Hz, 2 H), 1.74 (dd, *J* = 12.7, 6.7 Hz, 1 H), 1.33 (s, 9 H), 1.17 (t, *J* = 7.6 Hz, 3 H), 0.91 (dd, *J* = 16.2, 6.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.8, 166.8, 74.0, 73.5, 67.3, 51.4, 51.0, 32.7, 28.9, 21.8, 18.5, 18.2, 10.7.

MS (ESI): *m*/*z* = 340.5 [M + 1].

(*R*)-*N*-(*tert*-Butyl)-2-(dibenzylamino)-2-[(2*R*,3*S*)-3-isopropyl-1-nicotinoylaziridin-2-yl]acetamide (Table 1, entry 14)
Yield: 19.1 mg (81%); dr = 4:1; pale solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.07 (d, *J* = 1.4 Hz, 1 H), 8.66 (dd, *J* = 4.8, 1.7 Hz, 1 H), 8.20 (dt, *J* = 8.0, 1.9 Hz, 1 H), 7.43–7.30 (m, 11 H), 6.38 (s, 1 H), 4.86 (dd, *J* = 6.2, 5.4 Hz, 1 H), 4.38 (dd, *J* = 6.3, 5.1 Hz, 1 H), 3.95–3.83 (m, 4 H), 3.15 (d, *J* = 5.2 Hz, 1 H), 1.95–1.81 (m, 1 H), 1.36 (s, 9 H), 1.07 (d, *J* = 6.8 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.1, 172.2, 168.4, 160.1, 151.9, 149.4, 138.7, 135.8, 129.1, 128.9, 128.6, 128.5, 127.7, 124.2, 123.2, 79.3, 76.0, 66.2, 55.4, 53.3, 51.4, 33.0, 29.0, 19.1, 17.7.

MS (ESI): *m*/*z* = 499.9 [M + 1].

(*R*)-*N*-Benzyl-2-{(2*R*,3*S*)-3-isopropyl-1-[2-(thiophen-3-yl)acetyl]aziridin-2-yl}-2-(piperidin-1-yl)acetamide (Table 1, entry 15)
Yield: 15.3 mg (90%); dr = 1.8:1; yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.30 (m, 2 H), 7.25 (d, *J* = 1.8 Hz, 1 H), 7.20–7.15 (m, 2 H), 7.10–7.08 (m, 1 H), 6.99 (ddd, *J* = 8.1, 4.9, 1.3 Hz, 2 H), 6.72 (s, 1 H), 4.64 (d, *J* = 10.0 Hz, 1 H), 4.53 (dd, *J* = 6.5, 4.8 Hz, 1 H), 4.37 (d, *J* = 6.1 Hz, 1 H), 4.28 (d, *J* = 5.8 Hz, 1 H), 4.16–4.10 (m, 2 H), 4.07 (d, *J* = 6.4 Hz, 1 H), 3.78 (dd, *J* = 8.7, 5.3 Hz, 1 H), 2.79 (d, *J* = 4.8 Hz, 1 H), 2.68 (dd, *J* = 10.4, 5.6 Hz, 2 H), 2.53 (d, *J* = 7.5 Hz, 4 H), 1.80–1.72 (m, 1 H), 1.26 (t, *J* = 7.1 Hz, 2 H), 0.94–0.89 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2, 169.2, 138.6, 135.3, 128.8, 128.6, 127.9, 127.5, 125.5, 122.5, 78.3, 74.8, 52.1, 50.5, 48.7, 43.2, 38.5, 32.7, 31.0, 29.7, 26.5, 24.3.

MS (ESI): *m*/*z* = 440.3 [M + 1].

(*S*)-Ethyl 2-{2-[1-(2-Bromobenzoyl)-3-isopropylaziridin-2-yl]-2-(pyrrolidin-1-yl)acetamido}-2-methylpropanethioate (Table 1, entry 16)
Yield: 14.7 mg (82%); dr = 1.1:1; pale oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80–7.75 (m, 1 H), 7.64 (dd, *J* = 3.6, 2.4 Hz, 1 H), 7.30–7.28 (m, 2 H), 4.63 (dd, *J* = 8.0, 3.4 Hz, 1 H), 4.31 (dd, *J* = 8.0, 5.9 Hz, 1 H), 2.93–2.88 (m, 3 H), 2.84 (dd, *J* = 7.4, 5.1 Hz, 7 H), 1.82 (dd, *J* = 8.4, 5.4 Hz, 8 H), 1.47 (s, 6 H), 1.40 (s, 5 H), 1.26–1.19 (m, 11 H), 1.04–0.99 (m, 8 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 193.5, 169.1, 161.1, 134.1, 132.0, 131.8, 131.7, 127.4, 127.1, 81.1, 74.2, 71.6, 62.4, 51.8, 32.9, 26.2, 24.7, 23.6, 18.7, 14.6.

MS (ESI): *m*/*z* = 525.4, 527.4 [M + 1].

2-[1-(2-Amino-4,5-difluorobenzoyl)-3-isopropylaziridin-2-yl]-*N*-(*tert*-butyl)-2-morpholinoacetamide (Table 1, entry 17)
Yield: 14.4 mg (72%); dr = 3:1; pale brown solid.

^{1}H NMR (400 MHz, MeOD): δ = 7.39 (ddd, *J* = 11.7, 9.0, 5.5 Hz, 1 H), 6.58 (ddd, *J* = 17.8, 12.9, 6.8 Hz, 1 H), 4.34 (d, *J* = 5.5 Hz, 1 H), 3.68 (dd, *J* = 10.2, 5.6 Hz, 2 H), 3.16 (dd, *J* = 5.5, 3.1 Hz, 1 H), 2.97–2.86 (m, 2 H), 2.69–2.58 (m, 4 H), 2.33 (dd, *J* = 7.3, 3.0 Hz, 1 H), 1.61 (dt, *J* = 13.6, 6.8 Hz, 1 H), 1.28–1.25 (m, 9 H), 1.11–1.01 (m, 6 H).

^{13}C NMR (100 MHz, MeOD): δ = 173.9, 170.3, 145.8, 119.7, 116.8, 106.0, 105.8, 105.5, 85.30, 68.1, 54.8, 46.9, 45.0, 31.3, 28.8, 20.2, 19.4.

^{19}F NMR (377 MHz, MeOD): δ = –135.8 (ddd, *J* = 21.9, 12.7, 8.8 Hz), –136.7 (ddd, *J* = 22.2, 12.7, 9.2 Hz).

MS (ESI): *m*/*z* = 439.3 [M + 1].

***N*-{(*S*)-1-[(*S*)-Aziridin-2-yl]-2-(*tert*-butylamino)-2-oxoethyl}-*N*-benzylbenzamide (1)**
The title compound was prepared using benzylamine as the amine component according to the general procedure; yield: 29 mg (64%); dr = 1.3:1; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10–8.06 (m, 1 H), 7.93–7.89 (m, 1 H), 7.55 (t, *J* = 7.4 Hz, 1 H), 7.50–7.38 (m, 2 H), 7.36–7.28 (m, 2 H), 7.14 (d, *J* = 6.7 Hz, 1 H), 4.92–4.84 (m, 1 H), 4.11 (dd, *J* = 8.5, 7.2 Hz, 1 H), 3.79 (dd, *J* = 35.3, 13.3 Hz, 2 H), 3.21 (d, *J* = 6.6 Hz, 1 H), 1.33 (s, 9 H), 1.27 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 169.5, 132.8, 131.7, 130.1, 128.8, 128.6, 128.4, 128.3, 127.6, 80.2, 65.9, 57.6, 52.6, 50.8, 28.7.

MS (ESI): *m*/*z* = 366.6 [M + 1].

***N*-(2-Isopropyl-4-morpholino-5-oxotetrahydrofuran-3-yl)-3-phenylpropanamide (2)**
The substrate (from Table 1, entry 11; 26 mg, 0.065 mmol) was dissolved in CH_2Cl_2 (2 mL) and added to a vial containing silica gel (200 mg). The vial was heated to 40 °C for 2 h. The reaction mixture was then loaded onto a silica gel column, and the product was eluted by flash chromatography using hexanes and EtOAc; yield: 16.1 mg (72%); colorless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (dd, *J* = 9.4, 3.3 Hz, 2 H), 7.23–7.17 (m, 3 H), 5.55 (d, *J* = 9.0 Hz, 1 H), 4.58 (dd, *J* = 18.6, 8.9 Hz, 1 H), 3.79 (dd, *J* = 8.5, 5.0 Hz, 1 H), 3.66 (dd, *J* = 10.8, 6.1 Hz, 4 H), 3.49 (d, *J* = 10.0 Hz, 1 H), 2.98 (td, *J* = 7.2, 2.6 Hz, 2 H), 2.84–2.76 (m, 2 H), 2.57–2.50 (m, 4 H), 1.83 (td, *J* = 6.9, 5.0 Hz, 1 H), 0.95 (dd, *J* = 6.8, 4.8 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.8, 171.7, 140.4, 128.8, 128.5, 126.7, 67.1, 49.6, 49.0, 38.4, 31.4, 30.6, 28.9, 18.5, 16.6.

MS (ESI): *m*/*z* = 361.6 [M + 1].

***N*-(2-Isopropyl-4-morpholino-5-oxotetrahydrofuran-3-yl)propionamide (3)**
The substrate (from Table 1, entry 7; 12 mg, 0.035 mmol) was dissolved in CH_2Cl_2 (1 mL) and added to a vial containing silica gel

(0.1 g). The vial was heated to 40 °C for 2 h. The reaction mixture was then loaded onto a silica gel column, and the product was eluted by flash chromatography using hexanes and EtOAc; yield: 7.0 mg (70%); pale yellow solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.47 (d, *J* = 8.9 Hz, 1 H), 4.65 (dd, *J* = 18.8, 8.9 Hz, 1 H), 3.93 (dd, *J* = 8.6, 5.1 Hz, 1 H), 3.71 (t, *J* = 4.7 Hz, 4 H), 3.58 (d, *J* = 10.1 Hz, 1 H), 2.96–2.87 (m, 2 H), 2.69–2.61 (m, 2 H), 2.24 (q, *J* = 7.7 Hz, 2 H), 2.03–1.92 (m, 1 H), 1.17 (t, *J* = 7.6 Hz, 3 H), 1.02 (dd, *J* = 6.8, 1.5 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.4, 171.7, 67.2, 49.7, 49.2, 30.9, 30.0, 18.4, 16.9, 9.7.

MS (ESI): *m*/*z* = 285.1 [M + 1].

(*S*)-2-[(2*R*,3*S*)-1-Benzoyl-3-isopropylaziridin-2-yl]-*N*-(*tert*-butyl)-2-hydroxyacetamide (4)

The title compound was prepared from the starting materials used for the product from Table 1, entry 12 according to the general procedure for multicomponent reactions, with the omission of amine. The reaction was monitored by TLC (eluent: EtOAc) and LCMS. Aqueous workup was performed after a 16 h reaction time; yield: 13.7 mg (73%); dr = 2.1:1; colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13–8.10 (m, 1 H), 8.00–7.97 (m, 1 H), 7.59 (d, *J* = 7.4 Hz, 1 H), 7.44 (dd, *J* = 10.7, 4.3 Hz, 2 H), 6.40 (s, 1 H), 4.49 (t, *J* = 5.8 Hz, 1 H), 4.32 (t, *J* = 5.5 Hz, 1 H), 4.17 (d, *J* = 5.1 Hz, 1 H), 1.87 (dd, *J* = 12.9, 6.7 Hz, 1 H), 1.17 (s, 9 H), 0.99 (dd, *J* = 6.8, 4.7 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0, 166.4, 132.3, 130.2, 128.7, 128.6, 86.4, 71.5, 71.3, 51.4, 32.7, 28.5, 17.8, 16.9.

MS (ESI): *m*/*z* = 319.4 [M + 1].

(*S*)-*N*-(*tert*-Butyl)-2-hydroxy-2-[(2*R*,3*S*)-3-isopropyl-1-nicotinoylaziridin-2-yl]acetamide (5)

The title compound was prepared from the starting materials used for the product from Table 1, entry 14 according to the general procedure for multicomponent reactions, with the omission of amine. The reaction was monitored by TLC (eluent: EtOAc) and LCMS. Aqueous workup was performed after a 16 h reaction time; yield: 9.1 mg (44%); dr = 3:1; pale oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83–8.78 (m, 1 H), 8.37–8.31 (m, 1 H), 8.22–8.17 (m, 1 H), 7.45–7.36 (m, 2 H), 5.86 (s, 1 H), 4.93 (d, *J* = 7.5 Hz, 1 H), 3.29 (dd, *J* = 7.5, 3.3 Hz, 1 H), 2.84 (dd, *J* = 7.3, 3.2 Hz, 1 H), 1.87–1.80 (m, 1 H), 1.38 (s, 9 H), 1.04–0.99 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.7, 163.9, 154.3, 151.2, 137.5, 136.5, 123.5, 75.0, 52.1, 48.2, 42.3, 30.0, 28.7, 20.4.

MS (ESI): *m*/*z* = 320.6 [M + 1].

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