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Reaction of vinyl triflates of α-keto esters with primary amines: efficient synthesis of aziridine carboxylates☆

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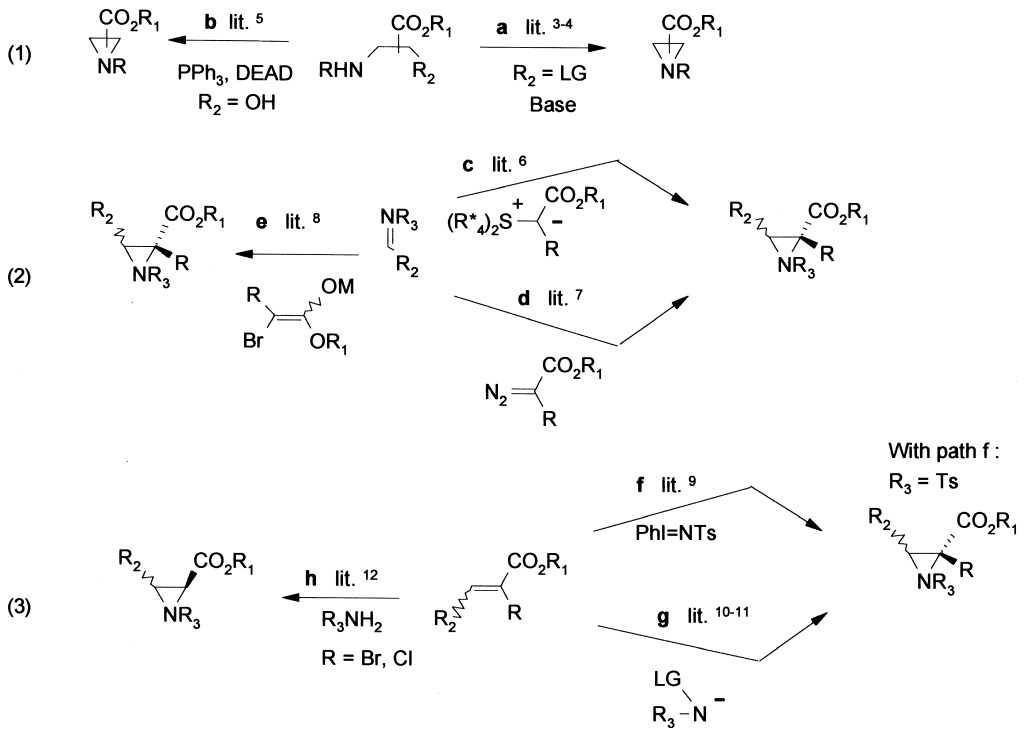
Abstract—Vinyl triflates of α-keto esters react smoothly with primary amines to provide aziridine carboxylates in good yields. In all cases, little or no stereoselectivity was observed. A mechanistic study has shown that aziridine carboxylates are strictly formed under kinetic control. The origin of this lack of stereoselectivity is explained by a non- or poorly stereoselective proton transfer.

1. Introduction

Due to their easy highly regio- and stereoselective ring opening reactions, aziridine 2-carboxylates have been shown to be valuable building blocks for the synthesis of a wide range of amine-containing biologically relevant molecules including α- and β-amino acids, β-amino alcohols, β-lactams and alkaloids.[2]



Scheme 1.

☆ For Part of this work see Ref. 1.

Keywords: aziridine carboxylates; vinyl triflates; α-keto esters.

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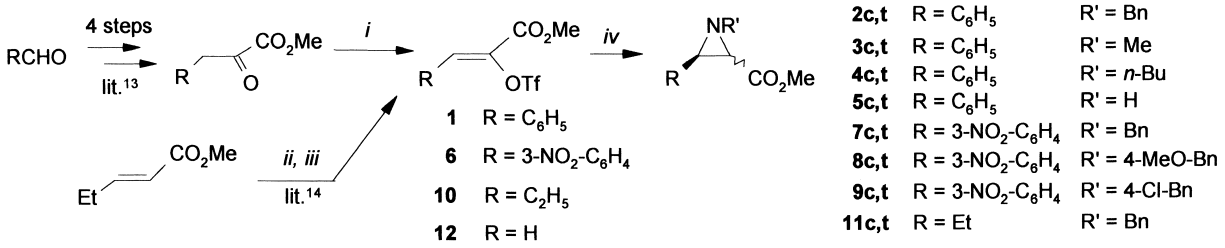


Scheme 2. (i) Tf_2O, iPr_2NEt, CH_2Cl_2, 0°C, 5 min, >85% (or NaH, THF, HMPA, $PhNTf_2$, 0°C, 5 min, >85%). (ii) cat. OsO_4, NMO, acetone/H_2O, 2 h, 20°C, 90%. (iii) Tf_2O 2.2 equiv., Pyr, 4.4 equiv., CH_2Cl_2, −80 to 0°C, 1 h, 93%. (iv) $R'NH_2$ 2 equiv., DMF or CH_3CN, 20°C.

Several methods are now well established for the synthesis of aziridine carboxylates (see Scheme 1).[2a,d] They are mainly based on three different routes: (1) nucleophilic displacement of nitrogen with removal of a leaving group (LG) at the α-position (paths a, b),[3–5] (2) 1,2-addition of carbon to imines (paths c–e),[6–8] and (3) 1,2-addition of nitrogen to conjugated esters (paths f–h).[9–12]

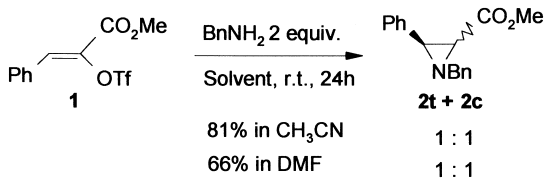
In the last category (3), the sequential conjugate addition-intramolecular nucleophilic substitution of primary amines to α-bromo or chloro enoates is one of the most interesting routes in terms of simplicity, mild reaction conditions and atom economy (path h).[12] Such reactions can have long reaction times and moderate yields. Moreover, synthesis of halogeno enoates may be tedious (use of toxic materials, lack of generality). We have recently started investigating tandem reactions of vinyl triflates of α-keto esters.[13] Due to the superior LG properties of the triflate group over bromine or chlorine atoms, we felt that this unexplored class of compounds may be aziridinated very mildly and efficiently. We report herein a consistent set of results which corroborate this expectation.

2. Results

Four representative vinyl triflates (**1**, **6**, **10**, **12**) were tested. As depicted in Scheme 2, they were prepared either by direct triflation of the parent α-keto esters in the case of **1**, **6**, **12**[13] or by sequential dihydroxylation, bis triflation-regioselective elimination of triflic acid from the commercially available *trans*-methyl pentenoate (case of **10**).[14] The vinyl triflates were generally stable except the unsubstituted compound **12** which had to be used rapidly after its synthesis. They could be purified by flash chromatography (FC) and stored for months at room temperature (**1**, **6**) or in the freezer (**10**) without notable decomposition. Substituted vinyl triflates **1**, **6** and **10** were all *Z* stereomers. Our first aziridination experiments aimed at determining the best conditions for the reaction. The phenyl triflate **1** and benzylamine were chosen as model partners, and the reactions were conducted at room temperature. A second equivalent of the amine was used in order to trap triflic acid released during the reaction.

First, reaction monitoring conditions deserve several comments. We were unable to achieve direct titrations in the reaction medium since a majority of stereomeric mixtures of *trans* and *cis* aziridines obtained throughout this work could not be separated through GC/MS. The *cis*/*trans* ratios were evaluated on the crude mixture by ^1H NMR spectroscopy. In all cases, the individual yields of isolated aziridines correlated with the NMR ratios, showing that aziridines are not stereochemically labile during the purification.

Various solvents were investigated. All reactions afforded *trans* and *cis* aziridine carboxylates **2t–c** in equal amounts (1/1 ratios). Only the reactions carried out in polar aprotic solvents such as DMF or CH_3CN provided a clean and sluggish transformation (Scheme 3).[15] The superior yield obtained in CH_3CN may be ascribed to partial loss of aziridines during evaporation of DMF under high vacuum. The reaction times given in Scheme 3 are not indicative of rate since the times were not optimized. However, GC/MS analysis of the reaction conducted in CH_3CN revealed an incomplete conversion after 5 h (40%).



Scheme 3.

A clean but very slow reaction took place in dichloromethane. When the reaction was carried out in THF, transformation of **1** was markedly retarded and several side-products were formed. The same trend was observed with MeOH, a yet usual solvent in similar aziridination of α-halo enoates.[12] In contrast to recent results on the related aziridination of triflate lactones,[15] exchanging triethylamine for benzylamine as triflic acid scavenger did not affect the reaction profile.

After optimizing the solvent, other substrates (**1**, **6**, **10**) were evaluated (Table 1). The reactions of **1** and **10** proceeded sluggishly (runs 1–3, 7, 8). On the other hand, the nitro triflate **6** was very reactive (runs 4–7), proving that electronic effects are important contributors to reaction rate. While **1** was aziridinated equally well in acetonitrile and DMF, only the latter allowed rapid reaction of triflates **6** and **10** (run 7 versus 8). The results depicted in Table 1 clearly show that the reaction consistently suffers from poor stereoselectivity (runs 1–4, 7, 8). Neither the concentration (run 2 versus 3) nor the substitution pattern of the olefinic bond (aryl versus alkyl, runs 2, 7) turned out to be influential. On the other hand, the stereoselectivity was slightly dependent on electronic effects (runs 5, 6 versus 1, 2, 7) and, to a smaller extent, on temperature (run 4 versus 5,

Table 1. Influence of the vinyl triflates on the diastereoselectivity

Runs[a]	Substrates	Temperature	Time	Products **t/c**	Yields (%)[b]
1	**1**	0°C	50 h	**2t/2c** 1/1	66
2[c]	**1**	rt	24h[d]	**2t/2c** 1/1	81
3[e]	**1**	rt	12 h	**2t/2c** 1/1	–[f]
4	**6**	rt	10 min	**7t/7c** 1/1	89
5	**6**	0°C	10 min	**7t/7c** 2.5/1	78[g]
6	**6**	−40°C	10 h	**7t/7c** 2.5/1	–[f]
7[c,h]	**10**	rt	36 h	**11t/11c** 1/1	77
8	**10**	rt	3 h	**11t/11c** 1/1	–[f]

[a] Unless otherwise indicated, the reactions were conducted in DMF.
[b] Isolated yields.
[c] Reaction conducted in CH_3CN.
[d] Time not optimized.
[e] The reaction was performed on 50 mg of **1** in 0.5 ml of CH_3CN.
[f] No purification was attempted, the *cis*/*trans* ratio were evaluated only by ^1H NMR on the crude.
[g] The reaction was finished within less than 10 min but pursued for 5 h to address the purpose of reversibility (see Section 3).
[h] 2 equiv. of benzylamine were reintroduced after 24 h due to incomplete conversion.

6). Increasing the reaction time also revealed that the final products do not equilibrate (run 1 versus 2, run 5 versus 6).

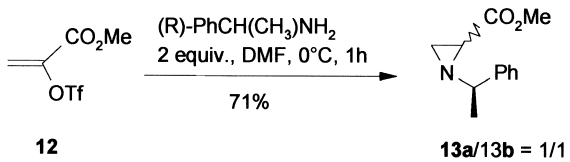
In order to expand this reaction in scope, a range of amines was investigated (Table 2). Hindered *tert*-butylamine and the moderately nucleophilic aniline were unproductive, even with the very reactive triflate **6** and under prolonged stirring (runs 5 and 9). On the other hand, *para*-substituted benzylamines as well as alkyl amines and NH_3 were good nucleophiles in this reaction (runs 1–3 and 7, 8). While the electronic nature of the amines seemed to play no role in the stereoselectivity (run 7 versus 8), their steric demand was slightly influential (runs 2–4).

It was envisaged that the use of chiral amines such as α-methyl benzylamine may induce a stereoselective aziridination process.[12e–g] Thus, (*R*)-phenylethylamine was reacted with the unsubstituted vinyl triflate **12**. Although the reaction stereoselectivity was disappointing, it is worth mentioning that aziridination of **12** went to completion within 1 h (time not optimized). This result indicates that previously unknown type **12** vinyl triflates of α-keto esters are very reactive and consequently hold promise as building blocks in organic synthesis (Scheme 4).

Table 2. Influence of the amines on the diastereoselectivity

Runs[a]	Substrates	Amines	Products **t/c**	Yields (%)[b]
1[c]	**1**	NH_3	**5t/5c** 1/1	65
2	**1**	$MeNH_2$	**3t/3c** 1/2	59
3	**1**	nBuNH$_2$	**4t/4c** 1/1.2	65
4[c]	**1**	$BnNH_2$	**2t/2c** 1/1	81
5[d]	**1**	tBuNH$_2$	No reaction	
6	**6**	$BnNH_2$	**7t/7c** 1/1	89
7	**6**	p-MeOBnNH$_2$	**8t/8c** 2/1	86
8	**6**	p-ClBnNH$_2$	**9t/9c** 2/1	77
9[d]	**6**	$PhNH_2$	No reaction	

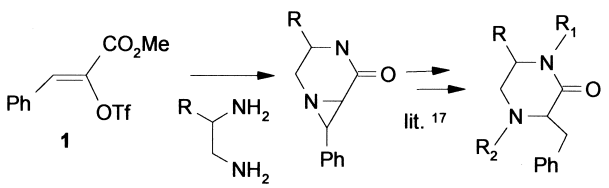
[a] Unless otherwise indicated, the reactions were conducted in DMF over 24 h at ambient temperature.
[b] Isolated yields.
[c] Reaction conducted in CH_3CN.
[d] The reaction was conducted over 72 h.



12 **13a/13b = 1/1**

Scheme 4.

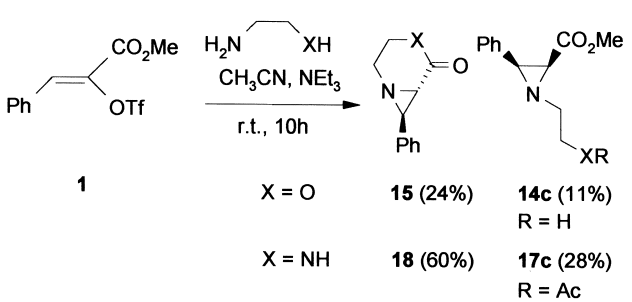
Tandem or cascade processes belong to a growing family of reactions allowing the regio- and stereocontrolled formation of several bonds and/or ring systems in a single step.[16] This triggered our interest in exploring the merit of some binucleophiles such as ethanolamine and ethylene diamine in this reaction. It was expected that lactone or lactame ring closure should ultimately follow the aziridine formation. In the case of using ethylene diamine, such a tandem process would be appealing for accessing a range of keto-piperazines, a class of compounds with potential biological properties (Scheme 5).[17]



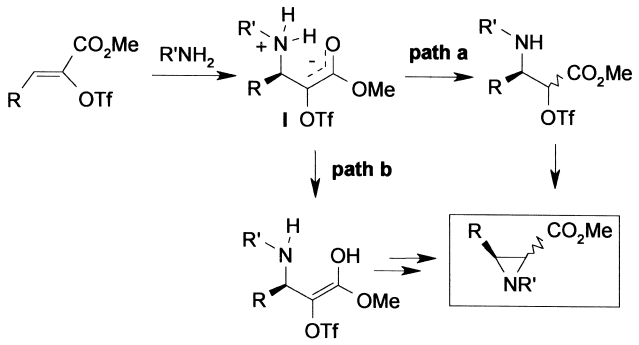
Scheme 5.

To our satisfaction, the expected tandem process did occur (Scheme 6). The reaction of **1** with ethanolamine gave the aziridine lactone **15** along with the *cis*-aziridine **14c**, yet moderate yields were obtained (24 and 11%, respectively). The ^1H NMR spectrum of the major product **15** exhibited two doublets at 2.78 and 3.67 ppm, respectively, with a small coupling constant value (J=2.3 Hz) attesting a *trans* relationship for the aziridinic protons. This product gave a molecular peak value of 189 in GC/MS, accounting for the bicyclic structure **15**. The ^1H NMR spectrum of the minor product exhibited the characteristic coupling constant value for a *cis* aziridine (δ_1=2.61 ppm, δ_2=3.03 ppm, J=7 Hz for the aziridinic protons). The presence of a singlet at 3.5 ppm as well as a molecular peak value of 221 in GC/MS accounted for the monocyclic structure **14c**.

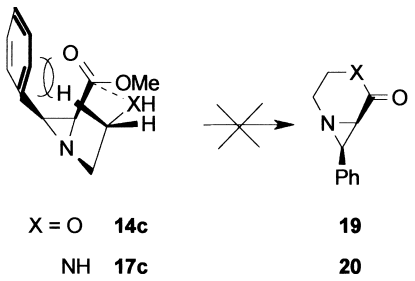
In contrast, a high-yielding reaction occurred between ethylene diamine and **1**. A 2/1 ratio of a fused bicyclic aziridine lactame **18** and the *cis* aziridine carboxylate **16c** was also obtained. The latter was isolated as its acetamide



Scheme 6.



Scheme 7.



Scheme 8.

17c after acetylation of the crude (Ac_2O, NEt_3). In this case the bicyclic product **18** was not responsive during GC/MS analysis, owing to a possible thermal instability of such a strained fused aziridine.[18]

3. Discussion

We have shown that the four α-alkoxycarbonyl vinyl triflates **1**, **6**, **10** and **12** examined in this study are very useful substrates for the formation of aziridine 2-carboxylates. The reactions proceeded moderately to quickly, and yields were good to excellent. Unfortunately, the reaction consistently suffered from a poor stereoselectivity. On the basis of literature precedents on related aziridination of α-halo enoates, we believe that a non-stereoselective proton transfer to a zwitterionic intermediate **I** is the most plausible rationale accounting for this lack of selectivity (Scheme 7).[19] The fact that reactions worked well only in polar aprotic solvents corroborates a stepwise mechanism with stabilization of the developing charges by such solvents.[20] This may further be supported by the marked color change observed when benzylamine was added to the very reactive triflate **6** (Table 1, runs 4–6).

Although we observed no equilibration of aziridines **2t–c** with time (Table 1, runs 1 versus 2), thermodynamic control can be questioned regarding the 1/1 ratios generally obtained. Although being less probable than the non-stereoselective proton transfer route (Scheme 7) this hypothesis needed some experiments to be definitively ruled out. First, vinyl triflate **1** and benzylamine were reacted in dichloromethane for 24 h. A TLC control indicated a low conversion, with clean formation of the aziridines **2t** and **2c**. A careful examination of the crude mixture by ^{1}H NMR spectroscopy revealed a 5/1/1 ratio of products **1/2t/2c** with signals corresponding to only *Z* stereochemistry of the starting triflate **1** being observed. This provides evidences against *Z* to *E* isomerization of the starting triflate due to possible reversibility of the Michael reaction.[21]

A second set of experiments was next directed toward evaluating the possibility of epimerization of aziridines. Each of the four aziridines **2t**, **2c**, **7t** and **7c** were individually stirred in the presence of benzylammonium triflate (1 equiv.) and benzylamine (0.1 equiv.) in DMF. After 24 h, no trace of the respective isomers **2c**, **2t**, **7c** and **7t** was detected either on TLC control or by ^{1}H NMR experiments. These results support a kinetically controlled formation of *cis* and *trans* aziridines. As well, it appears unlikely that equilibration had taken place by the time we measured the observed ratios. The latter mirrors the stereochemical profile of the protonation which is, therefore, the unique key stereodifferentiating step (Scheme 7).

The reactions between binucleophilic ethanolamine or ethylene diamine and **1** proceeded with somewhat higher stereoselectivity than related reactions involving simpler amines (Scheme 3, Table 1, runs 1, 2 and Table 2, runs 1, 2 and 4). This selectivity is surprising and as yet an unclear result.

In these reactions, only bicyclic structures of *trans* stereochemistry were obtained. Such discrimination could be explained by steric clash between the phenyl group and an hydrogen of the aminoalkyl chain in the ring closing transition state of the *cis* aziridine carboxylates (Scheme 8).

4. Conclusion

In summary, we have developed a straightforward procedure to produce aziridine 2-carboxylates by reacting various primary amines with a range of 1-alkoxycarbonyl vinyl triflates. The reactions generally proceeded smoothly, and yields were good to excellent. The mechanistic rationale of the reaction is proposed to involve Michael addition of the amine followed by either direct C-enolate protonation or sequential O-enolate protonation, enol–ester tautomery and finally internal displacement of the triflate group. The reaction proceeded with poor diastereoselectivity due to non-stereoselective protonation.

Further work aiming at getting a deeper insight into the key diastereodifferentiating protonation step, and toward developing a chiral, broadly applicable version of this reaction is currently underway in our laboratory.

5. Experimental

5.1. General

All melting points were measured on a Boetius micro hotstage and are uncorrected. ^{1}H and ^{13}C NMR spectra were

recorded respectively at 200 and 50 MHz. The infrared spectra were recorded on a Perkin–Elmer FT-IR paragon 1000 spectrometer. Thin-layer chromatographies (TLC) were performed with aluminum plates (0.20 mm) precoated with fluorescent silica gel, using EtOAc/hexanes as eluent. Reaction components were then visualized under UV light and dipped in a Dragendorff solution. Silica gel (230–400 mesh) was used for FC separations. Gas chromatography–mass spectrometry (GC–MS) was performed with a GC apparatus equipped with a 25 m capillary column, at 90°C for 2 min, then 10°C min^{-1} up to 290°C. All reactions were performed under an inert atmosphere. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt St Aignan, France.

Spectroscopic data of aziridine carboxylates **2c**, **t**,[12e,23] **3c**, **t**,[22] **5c**, **t**,[23] **11c**, **t**,[23] **13a**, **b**[24] have already been described. Perfect correlations were found between our ^1H NMR spectra and those reported.

5.2. General procedures for preparation of 2-trifluoromethanesulfonyloxy methyl propenoates

5.2.1. Procedure A: synthesis of vinyl triflates 1, 6, 12. Anhydrid trifluoromethanesulfonic (1 equiv.) was added dropwise under an argon atmosphere at 0°C to a stirred solution of the requisite α-keto ester (1 equiv.) in anhydrous dichloromethane (10 ml $mmol^{-1}$). Freshly distilled diisopropylethylamine (DiPEA, 1 equiv.) was immediately added dropwise to the resulting purple solution. After stirring for 15 min, dichloromethane was carefully evaporated and the residue was dissolved with a volume (7.5 ml $mmol^{-1}$) of a solution containing diethyl ether (2/3) and dichloromethane (1/3). This suspension was kept in a cold bath (0°C) for 1 h and the residual ammonium salt was filtered off on a path of Celite. After two washings with water, the organic phase was dried over sodium sulfate and concentrated. The resulting products were purified as follows: **1** was allowed to stir for 5 min in ethanol (5 ml $mmol^{-1}$), filtered off, washed with cold ethanol and dried under high vacuum. **3** and **7** were purified by FC using hexane/EtOAc 7/3 as the eluent.

5.2.2. Procedure B: synthesis of vinyl triflates 6. A commercially available solution of NaHMDS 1 M in THF (1 equiv.) was added dropwise under an argon atmosphere at 0°C to a stirred solution of the requisite α-keto ester (1 equiv.) in anhydrous tetrahydrofurane (5 ml $mmol^{-1}$). After 5 min, a THF solution of hexamethylphosphoramide (3 equiv.) and *N*-phenyltriflimide (1 equiv.) in tetrahydrofurane (3 ml $mmol^{-1}$) was added dropwise. After 30 min, the solution was hydrolyzed with an aqueous solution of ammonium chloride (10 ml $mmol^{-1}$), the aqueous layer was extracted three times with diethyl ether, and the organic layer was washed twice with brine. After drying over sodium sulfate, filtration and evaporation of the solvents, the product was purified as indicated above.

5.2.3. Procedure C: synthesis of vinyl triflates 10. To a cold (−80°C) solution of (*E*)-2,3-dihydroxy-methyl pentenoate (1 g, 6.76 mmol) in dichloromethane (20 ml) were added dropwise simultaneously under an argon atmosphere anhydrid trifluoromethanesulfonic (2.5 ml, 2.2 equiv.) and pyridine (2.4 ml, 4.4 equiv.). The stirred mixture was allowed to slowly rise to 0°C, then dichloromethane was carefully evaporated and the residue was dissolved in 10 ml of diethyl ether. This suspension was kept in a cold bath (0°C) for 1 h and the residual ammonium salt was filtered off on a path of Celite. After two washings with 10 ml of water, the organic phase was dried over sodium sulfate and concentrated. The oily pale yellow product obtained was clean and could be used further without purification.

5.2.4. (*Z*)-3-Phenyl-2-trifluoromethylsulfonyloxy methyl propenoate (1). Yield=77%. White solid, mp 76°C. Anal. calcd for $C_{11}H_9F_3O_5S$: C, 42.58; H, 2.92. Found: C, 42.47; H, 3.16. EIMS *m/z* (rel int) 310 (M^+, 20%), 279 (5), 177 (17), 149 (43), 121 (base), 91 (61). ^1H NMR (200 MHz, $CDCl_3$) δ 3.92 (s, 3H), 7.42–7.45 (m, 3H), 7.53 (s, 1H), 7.60–7.65 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.3, 108.8 (CF_3), 115.1 (CF_3), 121.4 (CF_3), 127.7 (CF_3), 128.9, 129, 129.7, 130.5, 131.3, 135.1, 161.6.

5.2.5. (*Z*)-3-[3-Nitrophenyl]-2-trifluoromethylsulfonyloxy methyl propenoate (6). Yield=89%. White solid, mp 68°C. Anal. calcd for $C_{11}H_8F_3NO_7S$: C, 37.19; H, 2.27; N, 3.94. Found: C, 36.93; H, 2.43; N, 3.91. EIMS *m/z* (rel int) 355 (M^+, 27%), 324 (6), 194 (56), 166 (base), 89 (65). ^1H NMR (200 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.58 (s, 1H), 7.62 (t, *J*=8.1 Hz, 1H), 7.95 (d, *J*=8.1 Hz, 1H), 8.29 (dd, *J*=8.1, 2.1 Hz, 1H), 8.47 (d, *J*=2.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.7, 108.7 (CF_3), 115.1 (CF_3), 121.5 (CF_3), 125, 125.4, 127.9 (CF_3), 128.4, 130.1, 131.3, 135.7, 137, 148.4, 160.9.

5.2.6. (*Z*)-3-Ethyl-2-trifluoromethylsulfonyloxy methyl propenoate (10). Yield=93%. Pale yellow oil. Anal. calcd for $C_{11}H_8F_3NO_7S$: C, 32.06; H, 3.46. Found: C, 32.17; H, 3.33. EIMS *m/z* (rel int) 232 (M^+-31, 20%), 155 (12), 69 (base), 59 (46). ^1H NMR (200 MHz, $CDCl_3$) δ 1.11 (t, *J*=7 Hz, 3H), 2.35 (dq, *J*=7.8, 7 Hz, 2H), 3.84 (s, 3H), 6.77 (t, *J*=7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 20.1, 53.0, 108.8 (CF_3), 115.2 (CF_3), 121.6 (CF_3), 128 (CF_3), 136.7, 138, 160.7.

5.2.7. 2-Trifluoromethylsulfonyloxymethyl propenoate (12). Yield 83%. Pale yellow oil. ^1H NMR (200 MHz, $CDCl_3$) δ 3.89 (s, 3H), 5.84 (d, *J*=3.2 Hz, 1H), 6.33 (d, *J*=3.2 Hz, 1H).

5.3. General procedure for the aziridination reaction

To a solution of the appropriate vinyl triflate (1 equiv.) in dry dimethylformamide or acetonitrile (3 ml 100 mg^{-1}) the requisite primary amine (2 equiv.) was added dropwise at the temperature indicated in the text under an argon atmosphere. When TLC monitoring showed total disappearance of the vinyl triflate, the solvent was carefully evaporated. Ether and water (5 ml 100 mg^{-1} each) were added on the residue and the mixture was stirred for 15 min. The aqueous phase was extracted three times with ether, then the organic phase was washed with brine and dried over sodium sulfate. After concentration, the resulting crude products were checked by ^1H NMR (see text) and purified by FC.

5.3.1. (*trans*)-Methyl 1-*n*-butyl-3-phenyl aziridine carboxylate (4t). Colourless oil. Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6. Found: C, 72.25; H, 8.36; N, 6.21. EIMS *m/z* (rel int) 233 (M^+, 5%), 232 (28), 190 (60), 176 (36), 174 (base), 118 (69), 117 (73), 116 (69), 91 (73), 90 (47), 89 (44). IR (film) 1727 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, J=7.0 Hz, 3H), 1.10–1.60 (m, 4H), 2.68 (d, J=2.3 Hz, 1H), 2.77–3.04 (m, 2H), 3.10 (s_l, 1H), 3.75 (s, 3H), 7.18–7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14, 20.3, 32.1, 44.2, 48.3, 51.3, 52.1, 126.2, 127.5, 128.3, 138.5, 169.2.

5.3.2. (*cis*)-Methyl 1-*n*-butyl-3-phenyl aziridine carboxylate (4c). White solid, mp 41–42°C. Anal. calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6. Found: C, 72.12; H, 8.48; N, 6.08. EIMS *m/z* (rel int) 233 (M^+, 6%), 232 (32), 190 (61), 176 (39), 174 (base), 118 (70), 117 (74), 116 (66), 91 (76), 90 (47), 89 (45). IR ($CHCl_3$) 1746 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (t, J=7.8 Hz, 3H), 1.21–1.78 (m, 4H), 2.27 (ddd, J_1=6.3 Hz, J_2=8.6 Hz, J_3=11.7 Hz, 1H), 2.48 (d, J=7.0 Hz, 1H), 2.77 (ddd, J_1=6.3 Hz, J_2=8.6 Hz, J_3=11.7 Hz, 1H), 2.87 (d, J=7.0 Hz, 1H), 3.44 (s, 3H), 7.15–7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 14.0, 20.4, 31.4, 45.7, 48.0, 51.7, 60.5, 127.3, 127.6, 127.8, 135.3, 168.8.

5.3.3. (*trans*)-Methyl 1-benzyl-3-[*m*-nitrophenyl]aziridine carboxylate (7t). Colorless oil. Anal. calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.53; H, 5.19; N, 9.01. ^1H NMR (200 MHz, $CDCl_3$) δ 2.73 (d, J=1.6 Hz, 1H), 3.35 (d, J=1.6 Hz, 1H), 3.66 (s, 3H), 4.03 (d, J=13.3 Hz, 1H), 4.18 (d, J=13.3 Hz, 1H), 7.10–7.33 (m, 5H), 7.38 (t, J=7.8 Hz, 1H), 7.54 (t, J=7.8 Hz, 1H), 7.97–8.10 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.7, 47.0, 52.3, 54.7, 121.3, 122.5, 127.1, 128.0, 128.3, 129.3, 132.4, 138.4, 140.4, 148.3, 168.4.

5.3.4. (*cis*)-Methyl 1-benzyl-3-[*m*-nitrophenyl]aziridine carboxylate (7c). White solid, mp 103–105°C. Anal. calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.40; H, 5.08; N, 8.84. EIMS *m/z* (rel int) 312 (M^+, <1%), 221 (base), 166 (33), 91 (63). ^1H NMR (200 MHz, $CDCl_3$) δ 2.68 (d, J=6.3 Hz, 1H), 3.08 (d, J=7.0 Hz, 1H), 3.44 (s, 3H), 3.60 (d, J=13.3 Hz, 1H), 3.93 (d, J=13.3 Hz, 1H), 7.15–7.45 (m, 6H), 7.70 (d, J=7.0 Hz, 1H), 8.01 (dd, J_1= 2.3 Hz, J_2=9.4 Hz, 1H), 8.20 (t, J=2.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 45.9, 46.6, 52.0, 63.3, 122.6, 123.0, 127.6, 128.0, 128.5, 128.8, 134.1, 137.0, 137.1, 147.9, 167.9.

5.3.5. (*trans*)-Methyl 1-[*p*-methoxybenzyl]-3-[*m*-nitrophenyl]aziridine carboxylate (8t). Yellow solid, mp 81°C. Anal. calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.3; N, 8.18. Found: C, 63.02; H, 5.37; N, 8.08. IR ($CHCl_3$) 1728 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.75 (d, J= 1.6 Hz, 1H), 3.39 (d, J=1.6 Hz, 1H), 3.72 (s, 3H), 3.76 (s, 3H), 4.01 (d, J=14.1 Hz, 1H), 4.15 (d, J=13.3 Hz, 1H), 6.83 (d, J=7.8 Hz, 2H), 7.27 (d, J=7.6 Hz, 2H), 7.44 (t, J=7.8 Hz, 1H), 7.59 (d, J=7.8 Hz, 1H), 8.02–8.10 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.66, 47.03, 52.33, 54.08, 55.13, 113.7, 121.3, 122.5, 129.3, 129.4, 130.5, 132.4, 140.5, 148.3, 158.7, 168.5.

5.3.6. (*cis*)-Methyl 1-[*p*-methoxybenzyl]-3-[*m*-nitrophenyl]-aziridine carboxylate (8c). Yellow oil. Anal. calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.3; N, 8.18. Found: C, 63.08; H, 5.22; N, 8.31. IR (film) 1727 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.70 (d, J=6.3 Hz, 1H), 3.09 (d, J=7.0 Hz, 1H), 3.48 (s, 3H), 3.56 (d, J=12.5 Hz, 1H), 3.76 (s, 3H), 3.93 (d, J=13.3 Hz, 1H), 6.85 (d, J=8.6 Hz, 2H), 7.30 (d, J=8.6 Hz, 2H), 7.42 (t, J=7.8 Hz, 1H), 7.72 (d, J=7.8 Hz, 1H), 8.05 (dd, J_1=2.3 Hz, J_2=7.0 Hz, 1H), 8.23 (t, J=2.3 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 45.63, 46.34, 51.94, 55.18, 62.59, 113.9, 122.5, 123.0, 128.8, 129.0, 129.4, 134.1, 137.2, 147.9, 159.0, 168.0.

5.3.7. (*trans*)-Methyl 1-[*p*-chlorobenzyl]-3-[*m*-nitrophenyl]aziridine carboxylate (9t). White solid, mp 101–104°C. Anal. calcd for $C_{17}H_{15}N_2O_4Cl$: C, 58.88; H, 4.36; N, 8.08. Found: C, 58.68; H, 4.41; N, 8.09. EIMS *m/z* (rel int) 346 (M^+, 2%), 221 (base), 166 (36), 125 (59), 89 (38). IR ($CHCl_3$) 1728 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.77 (d, J=2.3 Hz, 1H), 3.39 (d, J=1.6 Hz, 1H), 3.71 (s, 3H), 4.05 (d, J=14.1 Hz, 1H), 4.21 (d, J=14.1 Hz, 1H), 7.22–7.32 (m, 4H), 7.46 (t, J=7.8 Hz, 1H), 7.60 (d, J=7.8 Hz, 1H), 8.10 (d, J=9.4 Hz, 1H), 8.13 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.60, 47.07, 52.41, 53.92, 121.2, 122.6, 128.5, 129.4 (2C), 132.4, 132.9, 136.9, 140.2, 148.3, 168.3.

5.3.8. (*cis*)-Methyl 1-[*p*-chlorobenzyl]-3-[*m*-nitrophenyl]-aziridine carboxylate (9c). Yellow solid, mp 98–100°C. Anal. calcd for $C_{17}H_{15}N_2O_4Cl$: C, 58.88; H, 4.36; N, 8.08. Found: C, 58.79; H, 4.43; N, 7.99. EIMS *m/z* (rel int) 346 (M^+, 3%), 221 (base), 166 (36), 125 (58), 89 (40). IR ($CHCl_3$) 1746 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.71 (d, J=7.0 Hz, 1H), 3.12 (d, J=7.0 Hz, 1H), 3.49 (s, 3H), 3.64 (d, J=13.3 Hz, 1H), 3.88 (d, J=13.3 Hz, 1H), 7.23–7.49 (m, 5H), 7.74 (d, J=7.8 Hz, 1H), 8.08 (d, J=9.4 Hz, 1H), 8.24 (s, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 45.98, 46.68, 52.03, 62.61, 122.7, 122.9, 128.7, 128.9, 129.2, 133.3, 134.0, 135.6, 136.9, 147.9, 167.7.

5.3.9. (*cis*)-Methyl 1-[2′-hydroxyethyl]-3-[phenyl]aziridine carboxylate (14c). Pale yellow oil. Anal. calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.09; H, 6.89; N, 6.2. EIMS *m/z* (rel int) 220 (M^+-1, 7%), 162 (44), 168 (43), 56 (base). IR ($CHCl_3$) 3430, 1731 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.61 (d, J=7.0 Hz, 1H), 2.72 (dd, J_1= 5.5 Hz, J_2=10.2 Hz, 2H), 3.03 (d, J=6.3 Hz, 1H), 3.50 (s, 3H), 3.82 (dd, J_1=5.5 Hz, J_2=10.2 Hz, 2H), 6.63 (s_l, 1H), 7.15–7.55 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 42.4, 45.5, 47.6, 51.9, 61.6, 127.5, 128.0, 128.5, 132.5, 168.7.

5.3.10. (*trans*)-Bicyclo [4,1,0]1-oxa-2-oxo-4-phenyl-5-aza heptane (15). Pale yellow oil. Anal. calcd for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.71; H, 5.98; N, 7.17. EIMS *m/z* (rel int) 189 (M^+, 46%), 172 (46), 117 (93), 90 (base). IR ($CHCl_3$) 1732 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.78 (d, J=2.3 Hz, 1H), 3.20–3.50 (m, 2H), 3.67 (d, J=2.3 Hz, 1H), 4.29 (dd, J_1=3.9 Hz, J_2=11.7 Hz, 1H), 4.48 (ddd, J_1=3.9 Hz, J_2=J_3=12 Hz, 1H), 7.18–7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 39.4, 41.5, 42.7, 62.7, 126.3, 128.3, 128.7, 135.8, 166.6.

5.3.11. (*cis*)-Methyl 1-[2′-*N*-acetylaminoethyl]-3-[phenyl]-aziridine carboxylate (17c). White solid, mp product instable upon heating. EIMS *m/z* (rel int) 263 (M^++1, 6%),

262 (M^+, 55), 247 (21), 219 (31), 203 (45), 185 (43), 161 (79), 143 (base), 91 (45). IR ($CHCl_3$) 3424, 1661 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.51 to 2.63 (m, 2H), 2.7–2.81 (m, 1H), 2.95 (d, J=7 Hz, 1H), 3.50–3.6 (m, 5H), 6.3 (s, large, 1H, NH), 6.63 (s_l, 1H), 7.19–7.28 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$+DMSO, d_6) δ 22.5, 45.0, 47.1, 51.3, 58.1, 65.2, 127.0, 127.4, 134.4, 167.9, 170.0.

5.3.12. (*trans*)-Bicyclo [4,1,0]1,5-diaza-2-oxo-4-phenyl heptane (18). Brown solid, mp product instable upon heating. EIMS *m/z* (rel int). Product instable in the column. IR ($CHCl_3$) 3410, 1660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 2.67 (t, J=2.3 Hz, 1H), 3.15–3.55 (m, 5H), 6 (s, large, NH), 7.18–7.40 (m, 5H). ^{13}C NMR (50 MHz, $CDCl_3$+DMSO, d_6) δ 35.5, 37.9, 42.3, 42.8, 125.8, 127.3, 127.6, 167.4.

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