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Synthesis and Functionalisation of 2,3-Diheterocycle-Substituted Aziridines

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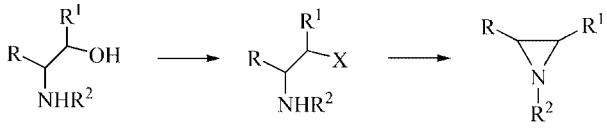
Polyfunctionalyzed aziridines each containing two heterocyclic moieties were prepared by Darzens reactions and the corresponding aziridinyl anions, generated by treatment with strong bases, were investigated. Coupling reaction with electrophiles allowed study of the configurational stability, highlighting the different stabilising effects of the heterocyclic substituents.

Introduction

Aziridines represent one of the most valuable three-membered ring systems in modern synthetic chemistry, because of their widely recognised versatility as significant intermediates for the synthesis of biologically and pharmacologically active compounds.[1,2] The large ring strain that characterises these small heterocycles favours highly regio- and stereocontrolled ring-opening reactions, affording modified amino acids and, more generally, nitrogen-containing organic compounds.[1,3,4]

A wide range of potential synthetic applications is possible with aziridines containing heterocyclic substituents, capable of freeing masked carbonyl functions.[5] Many synthetic approaches for the synthesis of aziridines have been reported in the literature, including reactions between nitrenes and olefins[6] or between carbenes and imines.[7] Preparative methodologies for chiral aziridines have been also extensively reviewed.[1a,8] Among the numerous synthetic methods, those that involve the cyclisation of β-amino alcohols seem to be particularly interesting (Scheme 1).[9]



X = Cl, Br, OSO_2Ph, etc.

Scheme 1.

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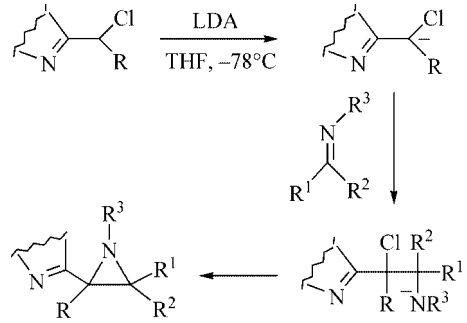
Our research group has recently developed a methodology for a simple and diastereoselective synthesis of several heterocycle-substituted aziridines based on Darzens reactions between α-chloroalkyl heterocycles and imines (Scheme 2).[10]



Scheme 2.

The functionalisation of these three-membered rings with different groups through the generation of the aziridinyl anion to form more complex aziridines is also very interesting. Many studies reported in the literature concern the chemistry of aziridinyl anions.[2b,11] Some of us recently reported the alkylation of *N*-(sulfonyloxazolinyl)aziridines through the formation of the corresponding aziridinyllithium species and subsequent trapping with electrophiles, which seems to proceed either with retention of configuration or with moderate stereoselectivity depending upon the starting isomers.[12] For these reasons we decided to investigate the synthesis of diheterocycle-substituted aziridines through coupling reactions between (α-chloroalkyl)oxazolinyllithium compounds and heteroaryl imines. We also describe the capture of the aziridinyl anions generated through the deprotonation of these aziridines by different electrophiles, together with the stereochemistry of these reactions, providing new polyfunctionalised aziridines.

Results and Discussion

Synthesis of Diheterocycle-Substituted Aziridines

The required (α-chloroalkyl)oxazolines **1** and **2** and the heteroarylidene-anilines **3**–**6**, prepared as described in the Exp. Section, were added to stirred solutions of lithium diisopropylamide (LDA) in THF at –78 °C, to produce the substituted aziridines **7**–**14** diastereoselectively and in satisfactory yields (55–72%), as reported in Table 1.

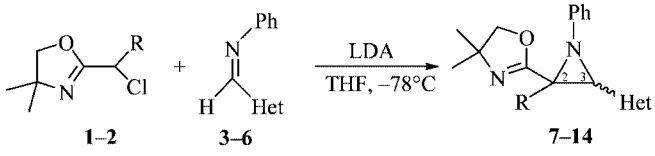
From each reaction, two diastereomers, (*R**,*S**) and (*R**,*R**), were isolated in variable ratios. With imines containing aza groups in their α positions (Table 1, Entries 1, 2, 5, 6, 8), the (*R**,*S**) arrangement was preferentially observed, while the (*R**,*R**) structure was favoured with the imine **4**, with the aza group in the γ position (Table 1, Entries 3, 4). The imine **6** did not react with the oxazoline **1**: only the product deriving from the homocoupling of the lithiated oxazoline **1** was isolated from the reaction mixture, as previously reported for analogous reactions.[13] For instance, the lithiated oxazoline **1** readily undergoes the homocoupling reaction together with the Darzens reaction, almost always lowering the yield of this latter. No homocoupling reaction was noticed, however, in the case of the lithiated oxazoline **2**, which is sterically more hindered than **1**. The imine **6** reacted in good yield with the oxazoline **2** in this case, affording the product **14**.

The (*R**,*S**) and (*R**,*R**) configurations were assigned on the basis of the ^{1}H NMR spectra, through the ^3J(H,H) coupling constants between the two protons on C2 and C3 for the products originating from **1** ($J_{cis} > J_{trans}$).[13] For compounds originating from **2** the relative configurations were assigned from the coupled ^{13}C NMR spectra: a very small or negligible ^3J(CH$_3$,H) coupling constant (≈ 0 Hz) corresponded to the (*R**,*S**) configuration, while a larger ^3J(CH$_3$,H) (≈ 2.5–3.3 Hz) corresponded to the (*R**,*R**) configuration.[14]

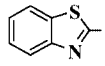
Functionalisation of Diheterocycle-Substituted Aziridines

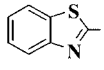
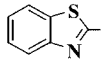
In principle, both the aziridinyl protons of **7** and **11** could be abstracted with strong bases, as the resulting aziri-

Table 1. Synthesis of diheterocycle-substituted aziridines **7**–**14**.



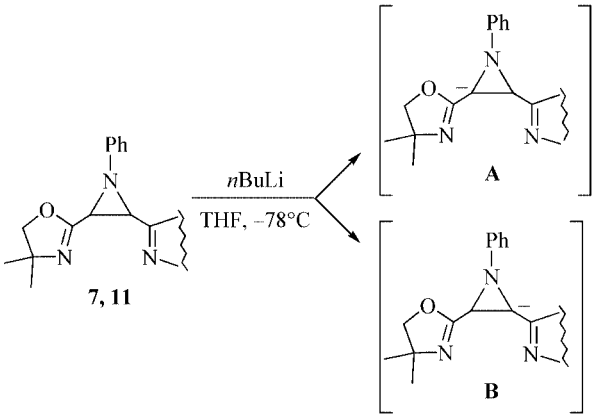
1: R = H; **2**: R = CH$_3$

3: Het =  ; **4**: Het =  ; **5**: Het =  ; **6**: Het = 

Entry	R	Het	Product	Total yield [%][a]	*dr*[b] (*R**,*S**)/(*R**,*R**)
1	H		**7**	55	55/45
2	CH$_3$		**8**	57	75/25
3	H		**9**	60	33/66
4	CH$_3$		**10**	55	33/66
5	H		**11**	63	55/45
6	CH$_3$		**12**	55	60/40
7	H		**13**	–	–
8	CH$_3$		**14**	72	90/10

[a] Isolated yields. [b] Diastereomeric ratios measured by GC and ^{1}H NMR spectroscopy.

dinyl anions (**A** and **B**, Scheme 3) should be stabilised by the presence of the two heterocyclic substituents.



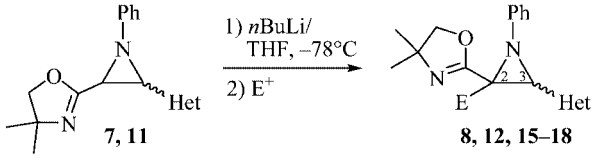
Scheme 3.

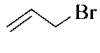
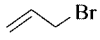
When a solution of *n*BuLi in hexanes was added to the aziridine **7** of (*R**,*S**) configuration dissolved in THF at –78 °C, with magnetic stirring and under a flow of N_2, an intensely red coloured solution was observed, indicating possible carbanion generation. The addition of CH_3OD after 20 min resulted in the decoloration of the solution. The workup of the reaction mixture gave the aziridine **15** as the only reaction product. The ^1H NMR and ^{13}C NMR spectra of **15** are identical to those of compound **7**, except for the signal of the proton bonded to the C2, which almost disappears, while the signal relating to the proton bonded to C3 becomes a singlet. It is therefore reasonable to assume that **15** still has the same (*R**,*S**) configuration as the starting aziridine **7** (Table 2, Entry 1).

A similar result was also obtained when (*R**,*S**)-**7**, deprotonated with *n*BuLi, was quenched with CH_3I; only compound **8**, with the same (*R**,*S**) configuration, was isolated in good yield (Table 2, Entry 2). The starting configuration was also retained when (*R**,*R**)-**7** was deprotonated and quenched with either CH_3OD or CH_3I (Table 2, Entries 3, 4). Compounds (*R**,*S**)-**11** and (*R**,*R**)-**11**, instead, underwent partial isomerisation in similar reactions, with (*R**,*S**)/(*R**,*R**) ratios of 70:30 and 30:70, respectively (Table 2, Entries 9–12). Surprisingly, with allyl bromide and benzyl bromide as electrophiles, the diastereomers of (*R**,*R**) configuration were the only reaction products isolated in both cases, when starting either from the aziridine (*R**,*S**)-**7** or from (*R**,*R**)-**7** (Table 2, Entries 5–8). The observed stereoselectivity could be due to the bigger electrophiles' steric hindrance, together with the π-interaction between the electrophile and the neighbouring heterocycle (2-pyridine). Aziridines **9** could not be deprotonated as they were isolated as inseparable mixtures of (*R**,*S**) and (*R**,*R**) diastereomers.

In no cases were compounds bearing different heterocycles and deriving from deprotonation of the aziridines at C3 isolated. The reported data show definitely that, of the

Table 2. Funtionalisation of diheterocycle-substituted aziridines **7** and **11**.

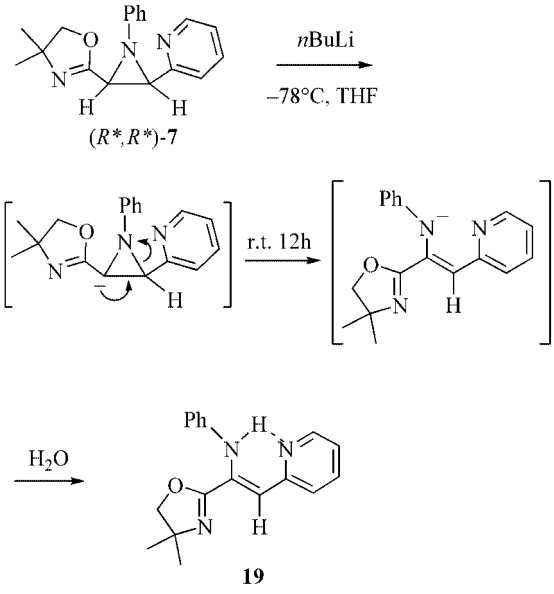


Entry	Substrate	Electrophile	Product	Total yield [%][a]	*dr*[b] (*R**,*S**)/(*R**,*R**)
1	(*R**,*S**)-**7**	CH_3OD	**15**	75	100/0
2	(*R**,*S**)-**7**	CH_3I	**8**	70	100/0
3	(*R**,*R**)-**7**	CH_3OD	**15**	65	10/90
4	(*R**,*R**)-**7**	CH_3I	**8**	65	0/100
5	(*R**,*S**)-**7**		**16**	65	0/100
6	(*R**,*S**)-**7**	$PhCH_2Br$	**17**	70	0/100
7	(*R**,*R**)-**7**		**16**	70	0/100
8	(*R**,*R**)-**7**	$PhCH_2Br$	**17**	75	0/100
9	(*R**,*S**)-**11**	CH_3OD	**18**	80	70/30
10	(*R**,*S**)-**11**	CH_3I	**12**	80	70/30
11	(*R**,*R**)-**11**	CH_3OD	**18**	80	30/70
12	(*R**,*R**)-**11**	CH_3I	**12**	75	30/70

[a] Isolated yields. [b] Diastereomeric ratios measured by GC and ^1H NMR spectroscopy.

two aziridinyl protons, the one bonded at C2, which bears the oxazoline as the heterocycle, is the more acidic.

In order to study the stabilities of the aziridinyl anion isomers, the product (*R**,*R**)-**7** was treated with *n*BuLi in THF at –78 °C, allowed to warm to room temperature and then stirred for 12 h. Aqueous quenching of the reaction mixture afforded the ring-opening product **19** presumably by the mechanism shown in Scheme 4.



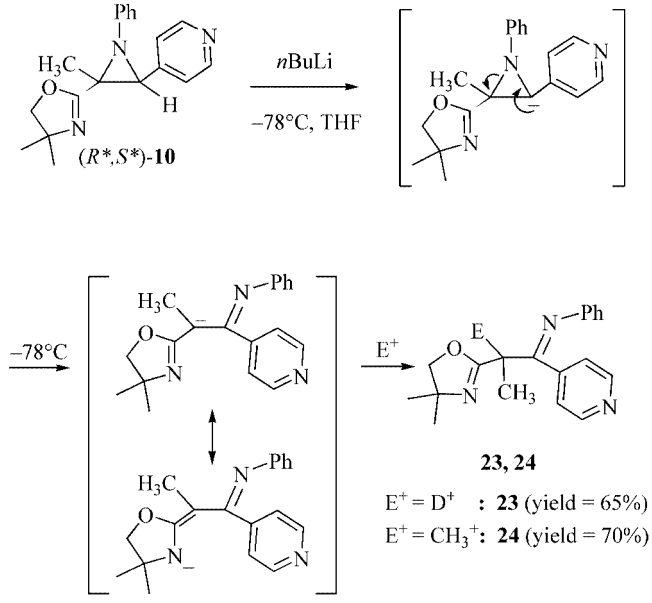
Scheme 4.

The aziridinyl anion generated from the (*R**,*S**)-**7** isomer, however, seemed to be more stable, as the deprotonation carried out under the conditions described above almost exclusively afforded the starting product. The additional stabilising chelation of the lithiated species by the aza group of the pyridinyl moiety has to be considered.

However, it was possible to functionalise the aziridinyl carbon C3, but only in the absence of protons at C2 (Table 3). The functionalisation of the C3 position was carried out with CH_3OD under the same conditions as reported for C2 and the results are collected in Table 3.

From the (*R**,*R**) substrates (Table 3, Entries 2 and 4), diastereomeric mixtures of (*R**,*S**)/(*R**,*R**) aziridines were obtained in a ratio of approximately 2:1, while from the (*R**,*S**) substrates (Table 3, Entries 1, 3, 5) only aziridines with retention of configuration (with respect to the starting aziridines) were isolated. In each case a strong tendency to form the thermodynamically more stable aziridine (*R**,*S** configuration) was observed.

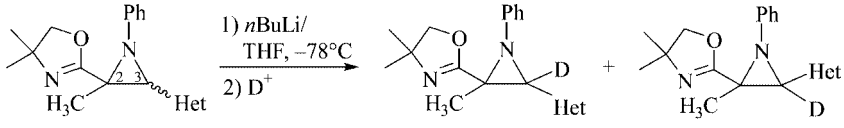
No products of functionalisation were isolated after treatment of (*R**,*S**)-**10** with CH_3OD: the substrate underwent ring-opening to afford the product **23**, presumably by the mechanism shown in Scheme 5.



Scheme 5.

Alkylation of (*R**,*S**)-**10** with CH_3I again afforded an analogous ring-opening product **24** (Scheme 5). This behaviour could be due to the lower stabilisation effect of the γ-aza-heterocycle (4-pyridine) on the aziridinyl anion, with respect to the α-aza-heterocycles (2-pyridine, 4-methylthiazole, or benzothiazole), resulting in the opening of the aziridinic ring.

Table 3. Funtionalisation of diheterocycle-substituted aziridines **8**, **12** and **14**.



Entry	Substrate	Product	Total yield [%][a]	*dr*[b] (*R**,*S**)/(*R**,*R**)	% D
1	(*R**,*S**)-**8**	**20**	75	100:0	75
2	(*R**,*R**)-**8**	**20**	75	70:30	70
3	(*R**,*S**)-**12**	**21**	65	100:0	83
4	(*R**,*R**)-**12**	**21**	70	65:35	70
5	(*R**,*S**)-**14**	**22**	65	100:0	81

[a] Isolated yields. [b] Diastereomeric ratios measured by GC and ^1H NMR spectroscopy.

Conclusions

In this paper we have described the synthesis of aziridines containing two heterocyclic moieties as substituents. Lithiated aziridines derived from these by deprotonation proved to be sufficiently stable to be trapped with electrophiles. The diastereoselectivity of the trapping reaction ranged from good to excellent. Such a high diastereoselectivity is indicative of the configurational stability of the above aziridinyllithiums. It is remarkable that the stabilising effect of the oxazoline ring on the lithiated aziridines proved to be higher than those of the other heterocycles investigated.

Experimental Section

General Remarks: *n*BuLi was a commercial solution in hexanes (Aldrich) and was titrated with *N*-pivaloyl-*o*-toluidine prior to use.[15] THF, pyridine-2-carboxaldehyde, pyridine-4-carboxaldehyde, 4-methylthiazole, 2-aminothiophenol, glycolic acid, lithium diisopropylamide (LDA), CH_3OD, methyl iodide and all other chemicals were of commercial grade (Aldrich), and were used without further purification. The (α-chloromethyl)oxazoline **1** and the (α-chloroethyl)oxazoline **2** were prepared by chlorination[16] of the commercial 2-methyl- and 2-ethyl-2-oxazolines (Aldrich). The heteroarylidene-anilines **3**–**6** were prepared by coupling of aniline with the appropriate heteroaryl carboxaldehydes[17] by Taguchi's procedure.[18] Petroleum ether refers to the 40–60 °C boiling fraction. The ^1H and the ^{13}C NMR spectra were recorded on a Bruker Avance 400 apparatus (400.13 MHz and 100.62 MHz, for ^1H and ^{13}C, respectively), with $CDCl_3$ as solvent and TMS as internal standard (δ = 7.24 for ^1H spectra; δ = 77.0 for ^{13}C spectra). The IR spectra were recorded on a Perkin–Elmer Model 283 spectrometer. GC-MS analyses were performed with a Shimadzu-17A gas chromatograph (5% diphenyl/95% dimethylpolysiloxane capillary column, 30 m, 0.25 mm i.d.), fitted with a Shimadzu GCMS-QP5050A mass-selective detector operating at 70 eV (EI). The electrospray ionisation (HR-ESI-MS) experiments were carried out on a hybrid Q*q*TOF mass spectrometer (PE SCIEX-QSTAR) fitted with an ion spray ionisation source. MS(+) spectra were acquired by direct infusion (5 μL min^{-1}) of a solution containing the appropriate sample (10 pmol μL^{-1}), dissolved in a solution of acetic acid (0.1%) in methanol/water 50:50 at the optimum ion voltage of 4800 V. The pressure of nitrogen gas flow was adjusted to 30 psi and the potentials of the orifice, the focusing ring and the skimmer were kept at 30, 50 and 25 V relative to ground, respectively. Melting points were determined with an electrothermal melting point apparatus and are uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was under UV light (254 nm). Column chromatography was performed on silica gel (63–200 mm) with use of petroleum ether/diethyl ether (Et_2O) mixtures as eluents. All reactions involving air-sensitive reagents were performed under nitrogen, in oven-dried glassware with use of syringe/septum cap techniques.

General Procedure for the Preparation of Diheterocycle-Substituted Aziridines 7–14: Compound **3**–**6** (1.5 mmol) dissolved in THF (5 mL) was added dropwise at –78 °C under nitrogen to a stirred solution of LDA (2.0 M in hexanes, 1 mL, 1.3 mmol) in THF (10 mL), followed by **1** or **2** (1.0 mmol) dissolved in THF (3 mL). After 20 min the resulting mixture was allowed to warm slowly to room temperature and then, after 3 h, quenched with H_2O. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 1:9) to afford the pure diheterocycle-substituted aziridines **7**–**14**, yields: 55–72%.

2-[3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-1-phenylaziridin-2-yl]-pyridine (7): (*R**,*S**)-**7** yield: 88 mg (30%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.12 (s, 3 H), 1.25 (s, 3 H), 3.56 (d, *J* = 8.1 Hz, 1 H), 3.59 (d, *J* = 2.5 Hz, 1 H), 3.82 (d, *J* = 8.1 Hz, 1 H), 4.06 (d, *J* = 2.5 Hz, 1 H), 6.94–6.98 (m, 3 H), 7.18–7.22 (m, 3 H), 7.37 (d, *J* = 7.4 Hz, 1 H), 7.65 (t, *J* = 7.4 Hz, 1 H), 8.55 (d, *J* = 4.2 Hz, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 28.0, 28.2, 41.8, 46.1, 67.4, 79.1, 120.2, 121.4, 122.7, 122.72, 128.6, 136.6, 148.7, 149.4, 156.0, 160.2 ppm. IR (film): $\tilde{\nu}$ = 3030, 2940, 1650, 1590, 1480, 1260 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 293 (18) [*M*]$^+$, 215 (74), 195 (100), 77 (69). HRMS calcd. for $C_{18}H_{19}N_3O$ 293.15297; found 293.15291. (*R**,*R**)-**7** yield: 73 mg (25%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.00 (s, 3 H), 1.17 (s, 3 H), 3.31 (d, *J* = 6.7 Hz, 1 H), 3.71–3.78 (m, 3 H), 6.96–7.06 (m, 3 H), 7.10–7.30 (m, 4 H), 7.66 (t, *J* = 7.4 Hz, 1 H), 8.56 (d, *J* = 4.2 Hz, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 28.1, 28.2, 41.4, 47.8, 67.2, 79.3, 120.0, 122.5, 122.6, 123.4, 129.1, 135.9, 148.9, 149.5, 155.3, 160.5 ppm. GC-MS (70 eV) *m*/*z* (%): 293 (19) [*M*]$^+$, 215 (71), 195 (100), 77 (83). IR (film): $\tilde{\nu}$ = 3030, 2940, 1660, 1570, 1480, 1360 cm^{-1}. HRMS calcd. for $C_{18}H_{19}N_3O$ 293.15297; found 293.15293.

2-[3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-methyl-1-phenylaziridin-2-yl]pyridine (8): (*R**,*S**)-**8** yield: 132 mg (43%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 1.00 (s, 3 H), 1.11 (s, 3 H), 1.36 (s, 3 H), 3.22 (d, *J* = 8.0 Hz, 1 H), 3.64 (d, *J* = 8.0 Hz, 1 H), 4.27 (s, 1 H), 6.88–6.92 (m, 3 H), 7.13–7.16 (m, 3 H), 7.43 (d, *J* = 7.6 Hz, 1 H) 7.62 (t, *J* = 7.6 Hz, 1 H), 8.55 (d, *J* = 4.5 Hz, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.4, 27.9, 28.3, 45.4, 50.1, 67.3, 78.7, 119.5, 122.1, 122.4, 122.5, 128.5, 136.4, 149.3, 149.5, 156.3, 162.2 ppm. IR (film): $\tilde{\nu}$ = 3025, 2920, 1660, 1600, 1420, 1260 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 307 (24) [*M*]$^+$, 118 (72), 77 (100), 65 (49). HRMS calcd. for $C_{19}H_{21}N_3O$ 307.16863; found 307.16861. (*R**,*R**)-**8** yield: 43 mg (14%), oil. ^1H NMR (400.13 MHz, $CDCl_3$): δ = 0.91 (s, 3 H), 1.05 (s, 3 H), 1.39 (s, 3 H), 3.50 (s, 1 H), 3.60–3.65 (m, 2 H), 6.93–6.98 (m, 3 H), 7.10–7.14 (m, 1 H), 7.18–7.22 (m, 2 H), 7.48 (d, *J* = 7.7 Hz, 1 H), 7.54 (t, *J* = 7.7 Hz, 1 H), 8.50 (d, *J* = 4.5 Hz, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.9, 28.0, 28.1, 46.1, 53.0, 67.1, 79.2, 120.4, 122.1, 122.4, 122.9, 128.9, 136.0, 147.8, 148.8, 156.0, 162.9 ppm. IR (film): $\tilde{\nu}$ = 3030, 2940, 1660, 1590, 1470, 1260 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 307 (23) [*M*]$^+$, 118 (78), 77 (100), 65 (52). HRMS calcd. for $C_{19}H_{21}N_3O$ 307.16863; found 307.16867.

4-[3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-1-phenylaziridin-2-yl]-pyridine (9): Inseparable mixture of two (*R**,*S**) and (*R**,*R**) configured diastereomers (*dr* = 33:66 by ^1H NMR). Overall yield: 175 mg (60%), oil. Distinguishable signals: (*R**,*S**)-**9**: ^1H NMR (400.13 MHz, $CDCl_3$): δ = 0.95 (s, 3 H), 1.04 (s, 3 H), 3.22 (d, *J* = 2.6 Hz, 1 H), 3.49 (d, *J* = 8.1 Hz, 1 H), 3.74 (d, *J* = 8.1 Hz, 1 H), 3.77 (d, *J* = 2.6 Hz, 1 H), 6.85–6.99 (m, 3 H), 7.18–7.21 (m, 2 H), 7.36 (d, *J* = 5.9 Hz), 8.48 (d, *J* = 5.9 Hz, 2 H) ppm. (*R**,*R**)-**9**: ^1H NMR (400.13 MHz, $CDCl_3$): δ = 0.98 (s, 3 H), 1.16 (s, 3 H), 3.22 (d, *J* = 6.6 Hz, 1 H), 3.43 (d, *J* = 6.6 Hz, 1 H), 3.61 (d, *J* = 8.1 Hz, 1 H), 3.68 (d, *J* = 8.1 Hz, 1 H), 6.85–6.99 (m, 3 H), 7.11–7.20 (m, 2 H), 7.35 (d, *J* = 5.9 Hz, 2 H), 8.48 (d, *J* = 5.9 Hz, 2 H) ppm. (*R**,*S**)-**9** + (*R**,*R**)-**9**: ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 27.9, 28.14, 28.18, 28.19, 43.04, 43.06, 43.72, 43.75, 67.4, 67.5, 79.20, 79.21, 119.9, 120.1, 121.7, 122.8, 123.1, 123.7, 128.8, 129.2, 144.1, 146.0, 148.2, 149.3, 149.8, 152.0, 159.5, 159.9 ppm. IR (film): $\tilde{\nu}$ = 3040, 2950, 1655, 1595, 1485, 1410, 1360, 1200 cm^{-1}. GC-MS

(70 eV) *m*/*z* (%): 293 (20) $[M]^+$, 238 (8), 215 (40), 134 (30), 104 (100), 77 (87). HRMS calcd. for $C_{18}H_{19}N_3O$ 293.15297; found 293.15294.

4-[3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-methyl-1-phenylaziridin-2-yl]pyridine (10): (*R**,*S**)-**10** yield: 58 mg (19%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.88 (s, 3 H), 1.12 (s, 3 H), 1.30 (s, 3 H), 3.34 (d, *J* = 8.0 Hz, 1 H), 3.65 (d, *J* = 8.0 Hz, 1 H), 4.10 (s, 1 H), 6.86–6.92 (m, 3 H), 7.12–7.16 (m, 2 H), 7.33 (d, *J* = 6.0 Hz, 2 H), 8.50 (d, *J* = 6.0 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.1, 27.8, 28.1, 45.7, 47.8, 67.2, 78.8, 119.6, 122.7, 122.9, 128.6, 145.2, 149.1, 149.5, 161.8 ppm. IR (film): $\tilde{\nu}$ = 3025, 2960, 1650, 1590, 1120 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 307 (11) $[M]^+$, 252 (14), 118 (100), 77 (63). HRMS calcd. for $C_{19}H_{21}N_3O$ 307.16863; found 307.16860. (*R**,*R**)-**10** yield: 110 mg (36%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.93 (s, 3 H), 0.98 (s, 3 H), 1.36 (s, 3 H), 3.25 (s, 1 H), 3.58–3.62 (m, 2 H), 6.88–6.95 (m, 3 H), 7.18 (t, *J* = 7.7 Hz, 2 H), 7.32 (d, *J* = 6.0 Hz, 2 H), 8.46 (d, *J* = 6.0 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.8, 28.1, 46.3, 50.4, 50.5, 67.2, 79.0, 120.1, 122.5, 122.9, 128.8, 144.7, 147.4, 149.1, 162.2 ppm. IR (film): $\tilde{\nu}$ = 3025, 2960, 1600, 1260, 1120 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 307 (6) $[M]^+$, 252 (6), 118 (100), 77 (60). HRMS calcd. for $C_{19}H_{21}N_3O$ 307.16863; found 307.16859.

4,4-Dimethyl-2-[3-(4-methylthiazol-2-yl)-1-phenylaziridin-2-yl]-4,5-dihydrooxazole (11): (*R**,*S**)-11 yield: 109 mg (35%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.23 (s, 3 H), 1.26 (s, 3 H), 2.44 (s, 3 H), 3.50 (d, *J* = 2.5 Hz, 1 H), 3.53 (d, *J* = 8.1 Hz, 1 H), 3.79 (d, *J* = 8.1 Hz, 1 H), 4.27 (d, *J* = 2.5 Hz, 1 H), 6.81 (s, 1 H), 6.98–7.01 (m, 3 H), 7.20–7.27 (m, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.0, 27.9, 28.2, 43.0, 43.5, 67.5, 79.1, 113.8, 120.1, 123.1, 128.7, 147.7, 153.2, 159.2, 162.8 ppm. IR (film): $\tilde{\nu}$ = 3025, 2920, 1650, 1590, 1480, 1260 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 313 (23) $[M]^+$, 215 (81), 104 (100), 77 (97). HRMS calcd. for $C_{17}H_{19}N_3OS$ 313.12507; found 313.12504. (*R**,*R**)-**11** yield: 88 mg (28%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.14 (s, 3 H), 1.23 (s, 3 H), 2.45 (s, 3 H), 3.33 (d, *J* = 6.3 Hz, 1 H), 3.83–3.86 (m, 3 H), 6.86 (s, 1 H), 7.03–7.11 (m, 3 H), 7.25–7.29 (m, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 17.0, 28.08, 28.11, 42.0, 44.7, 67.4, 79.4, 114.0, 119.8, 123.8, 129.1, 151.3, 152.9, 159.8, 165.2 ppm. IR (film): $\tilde{\nu}$ = 3025, 2920, 1660, 1590, 1480, 1210 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 313 (30) $[M]^+$, 215 (92), 104 (100), 77 (90). HRMS calcd. for $C_{17}H_{19}N_3OS$ 313.12507; found 313.12502.

4,4-Dimethyl-2-[2-methyl-3-(4-methylthiazol-2-yl)-1-phenylaziridin-2-yl]-4,5-dihydrooxazole (12): (*R**,*S**)-**12** yield: 108 mg (33%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.98 (s, 3 H), 1.10 (s, 3 H), 1.52 (s, 3 H), 2.40 (s, 3 H), 3.21 (d, *J* = 8.0 Hz, 1 H), 3.61 (d, *J* = 8.0 Hz, 1 H), 4.38 (s, 1 H), 6.79 (s, 1 H), 6.90–7.00 (m, 3 H), 7.10–7.17 (m, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.5, 17.2, 27.9, 28.2, 46.5, 47.1, 67.5, 78.8, 113.8, 119.4, 122.9, 128.6, 148.7, 153.6, 161.6, 166.8 ppm. IR (film): $\tilde{\nu}$ = 3030, 2960, 1640, 1600, 1120 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 327 (35) $[M]^+$, 228 (62), 174 (50), 118 (100), 77 (94). HRMS calcd. for $C_{18}H_{21}N_3OS$ 327.14073; found 327.14071. (*R**,*R**)-**12** yield: 72 mg (22%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.13 (s, 3 H), 1.18 (s, 3 H), 1.43 (s, 3 H), 2.46 (s, 3 H), 3.70 (s, 1 H), 3.82–3.84 (m, 2 H), 6.81 (s, 1 H), 7.00–7.05 (m, 3 H), 7.26–7.30 (m, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.8, 17.1, 28.05, 28.10, 47.2, 49.8, 67.4, 79.4, 113.6, 120.3, 123.3, 128.9, 146.9, 152.9, 162.4, 166.3 ppm. IR (film): $\tilde{\nu}$ = 3030, 2960, 1660, 1600, 1140 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 327 (33) $[M]^+$, 228 (36), 174 (49), 118 (100), 77 (90). HRMS calcd. for $C_{18}H_{21}N_3OS$ 327.14073; found 327.14070.

2-[3-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-methyl-1-phenylaziridin-2-yl]benzothiazole (14): (*R**,*S**)-**14** yield: 236 mg (65%) solid. M.p. 119–121 °C (*n*-hexane). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.06 (s, 3 H), 1.19 (s, 3 H), 1.66 (s, 3 H), 3.34 (d, *J* = 8.0 Hz, 1 H), 3.78 (d, *J* = 8.0 Hz, 1 H), 4.60 (s, 1 H), 6.99–7.03 (m, 3 H), 7.22–7.26 (m, 2 H), 7.39–7.42 (m, 1 H), 7.49–7.52 (m, 1 H), 7.89 (d, *J* = 7.7 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.7, 27.9, 28.2, 46.9, 47.4, 67.6, 79.0, 119.5, 121.7, 123.0, 123.1, 125.1, 126.2, 128.7, 134.9, 148.5, 154.0, 161.3, 168.8 ppm. IR (film): $\tilde{\nu}$ = 3030, 2960, 1660, 1600, 1140 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 363 (50) $[M]^+$, 229 (36), 174 (49), 118 (100), 77 (90). HRMS calcd. for $C_{21}H_{21}N_3OS$ 363.14073; found 363.14075. (*R**,*R**)-**14** yield: 25 mg (7%), solid. M.p. 110–112 °C (*n*-hexane). ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.09 (s, 3 H), 1.11 (s, 3 H), 1.48 (s, 3 H), 3.77–3.82 (m, 2 H), 3.83 (s, 1 H), 7.00–7.10 (m, 3 H), 7.27–7.32 (m, 2 H), 7.35–7.39 (m, 1 H), 7.45–7.49 (m, 1 H), 7.86 (d, *J* = 7.8 Hz, 1 H), 8.02 (d, *J* = 8.1 Hz, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 16.9, 28.1, 47.6, 49.9, 67.5, 79.5, 120.3, 121.5, 122.8, 123.5, 124.9, 125.9, 129.1, 134.9, 146.6, 153.6, 162.3, 168.6 ppm. IR (film): $\tilde{\nu}$ = 3030, 2960, 1660, 1590, 1120 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 363 (46) $[M]^+$, 229 (21), 190 (27), 118 (98), 77 (100). HRMS calcd. for $C_{18}H_{21}N_3OS$ 363.14073; found 363.14071.

General Procedure for the Functionalisation of Aziridines 7, 8, 10–12 and 14: *n*BuLi (2.5 M in *n*-hexane, 0.5 mL, 1.3 mmol) was added dropwise at –78 °C under nitrogen to a stirred solution of the starting aziridine (1 mmol) in THF (10 mL). The resulting mixture was stirred at –78 °C for 1 h, and the corresponding electrophile (1.5 mmol) was then added. The mixture was allowed to warm to room temperature and quenched with H_2O. The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O, 1:9) to afford the pure polyfunctionalised aziridines **15**–**18** (yields: 65–80%), **20**–**22** (yields: 65–75%) or the ring-opening products **23** and **24** (yields: 65%, 70%).

Deuterated compounds **15**, **18**, **20** and **21** with (*R**,*S**) and (*R**,*R**) configurations showed $[M]^+$ mass values greater by one than those reported for the starting (*R**,*S**)- and (*R**,*R**)-**7**, **11**, **8**, and **12**, respectively. Analogously, (*R**,*S**)-**22** showed a $[M]^+$ value greater by one than that reported for (*R**,*S**)-**14**. The ^{1}H NMR and ^{13}C NMR spectroscopic data for (*R**,*S**)- and (*R**,*R**)-**15** and **18** were the same as those reported for (*R**,*S**)- and (*R**,*R**)-**7**, and **11**, respectively, except that the signals of the protons bonded to C2 had almost disappeared, while the signals relating to the protons bonded to C3 had become singlets.

The ^{1}H NMR and ^{13}C NMR spectra of (*R**,*S**)- and (*R**,*R**)-**20** and **-21** and (*R**,*S**)-**22** were identical to those of (*R**,*S**)- and (*R**,*R**)-**8** and **-12** and (*R**,*S**)-**14**, respectively, except that the signals of the protons bonded to C3 had almost disappeared (Table 4).

Table 4. HRMS data for deuterated aziridines **15**, **18** and **20**–**22**.

Product	Molecular formula	Calculated	Found
(*R**,*S**)-**15**	$C_{18}H_{18}DN_3O$	294.15924	294.15926
(*R**,*R**)-**15**	$C_{18}H_{18}DN_3O$	294.15924	294.15927
(*R**,*S**)-**18**	$C_{17}H_{18}DN_3OS$	314.13134	314.13130
(*R**,*R**)-**18**	$C_{17}H_{18}DN_3OS$	314.13134	314.13132
(*R**,*S**)-**20**	$C_{19}H_{20}DN_3O$	308.17490	308.17489
(*R**,*R**)-**20**	$C_{19}H_{20}DN_3O$	308.17490	308.17492
(*R**,*S**)-**21**	$C_{18}H_{20}DN_3OS$	328.14700	328.14702
(*R**,*R**)-**21**	$C_{18}H_{20}DN_3OS$	328.14700	328.14703
(*R**,*S**)-**22**	$C_{21}H_{20}DN_3OS$	364.14700	364.14710

2-[2-Allyl-3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-1-phenylaziridin-2-yl]pyridine (16): (*R**,*R**)-**16:** yield: 233 mg (70%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.03 (s, 3 H), 1.10 (s, 3 H), 2.41–2.46 (m, 1 H), 2.53–2.58 (m, 1 H), 3.64 (s, 1 H), 3.69 (d, J = 8.0 Hz, 1 H), 3.79 (d, J = 8.0 Hz, 1 H), 5.02–5.09 (m, 2 H), 5.85–5.95 (m, 1 H), 6.96–7.08 (m, 3 H), 7.11–7.16 (m, 1 H), 7.18–7.25 (m, 2 H), 7.47 (d, J = 7.8 Hz, 1 H), 7.60 (t, J = 7.8 Hz, 1 H), 8.58 (d, J = 4.7 Hz, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 28.8, 28.1, 35.4, 49.7, 50.6, 67.3, 79.1, 118.4, 120.9, 121.7, 122.4, 123.0, 128.9, 132.9, 135.9, 147.4, 148.9, 156.1, 161.6 ppm. IR (film): $\tilde{\nu}$ = 3030, 2940, 1650, 1595, 1360, 1260 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 333 (23) $[M]^+$, 241 (100), 169 (21), 130 (15), 117 (17), 77 (19). HRMS calcd. for $C_{21}H_{23}N_3O$ 333.18429; found 333.18431.

2-[2-Benzyl-3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-1-phenylaziridin-2-yl]pyridine (17): (*R**,*R**)-**17:** yield: 287 mg (75%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 0.96 (s, 3 H), 1.04 (s, 3 H), 2.94 (d, J = 15.0 Hz, 1 H), 3.17 (d, J = 15.0 Hz, 1 H), 3.59 (d, J = 8.0 Hz, 1 H), 3.67 (d, J = 8.0 Hz, 1 H), 3.80 (s, 1 H), 7.04–7.09 (m, 3 H), 7.15–7.29 (m, 8 H), 7.44 (d, J = 7.8 Hz, 1 H), 7.58 (t, J = 7.8 Hz, 1 H), 8.59 (d, J = 5.0 Hz, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 27.9, 29.8, 58.4, 67.3, 67.6, 79.4, 119.5, 119.8, 119.9, 121.8, 123.9, 124.6, 128.7, 135.7, 136.1, 142.7, 147.0, 147.2, 147.7, 162.0 ppm. IR (film): $\tilde{\nu}$ = 3030, 2940, 2850, 1640, 1595, 1360, 1260 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 383 (65) $[M]^+$, 291 (100), 219 (58), 200 (50), 183 (70), 77 (40). HRMS calcd. for $C_{25}H_{25}N_3O$ 383.19995; found 383.19998.

[1-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-pyridin-2-ylvinyl]phenylamine (19): Yield: 161 mg (55%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.34 (s, 6 H), 3.93 (s, 2 H), 6.20 (s, 1 H), 6.93–7.02 (m, 4 H), 7.15 (d, J = 8.0 Hz, 1 H), 7.22–7.24 (m, 2 H), 7.55–7.60 (m, 1 H), 8.48 (d, J = 4.9 Hz, 1 H), 11.0 (s, broad, 1 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 27.9, 67.3, 79.5, 107.2, 119.6, 119.8, 121.8, 123.9, 128.7, 136.1, 141.0, 142.7, 147.7, 157.2, 161.6 ppm. IR (film): $\tilde{\nu}$ = 3380 (broad), 3024, 2969, 1633, 1599, 1500, 1120 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 293 (50) $[M]^+$, 215 (100), 194 (70), 77 (25). HRMS calcd. for $C_{18}H_{19}N_3O$ 293.15297; found 293.15295.

[2-Deutero-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-1-pyridin-4-ylpropylidene]phenylamine (23): Yield: 200 mg (65%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.36 (s, 6 H), 1.75 (s, 3 H), 3.93 (s, 2 H), 6.55 (d, J = 8.3 Hz, 2 H), 6.81 (t, J = 8.3 Hz, 1 H), 7.02 (t, J = 8.3 Hz, 2 H), 7.22 (d, J = 5.5 Hz, 2 H), 8.57 (d, J = 5.5 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 14.1, 28.8, 67.1, 77.3, 94.0, 121.3, 121.8, 124.7, 128.6, 141.4, 144.2, 147.0, 149.8, 165.2 ppm. IR (film): $\tilde{\nu}$ = 3030, 2950, 1635, 1600, 1590, 1350, 1280 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 308 (37) $[M]^+$, 182 (100), 77 (85). HRMS calcd. for $C_{19}H_{20}DN_3O$ 308.17490; found 308.17493.

[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-methyl-1-pyridin-4-ylpropylidene]phenylamine (24): Yield: 225 mg (70%), oil. ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.06 (s, 6 H), 1.53 (s, 6 H), 3.76 (s, 2 H), 6.49 (d, J = 7.7 Hz, 2 H), 6.72 (t, J = 7.7 Hz, 1 H), 6.84 (d, J = 5.7 Hz, 2 H), 7.00 (t, J = 7.7 Hz, 2 H), 8.34 (d, J = 5.7 Hz, 2 H) ppm. ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 15.2, 24.0, 28.0, 67.0, 79.1, 119.8, 123.1, 123.4, 128.4, 144.2, 149.7, 150.1, 167.7, 171.6 ppm. IR (film): $\tilde{\nu}$ = 3030, 2920, 1640, 1895, 1360, 1260 cm^{-1}. GC-MS (70 eV) *m*/*z* (%): 321 (5) $[M]^+$, 306 (2), 218 (6), 182 (100), 77 (8). HRMS calcd. for $C_{20}H_{23}N_3O$ 321.18429; found 321.18431.

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