HETEROCYCLES, Vol. 71, No. 6, 2007, pp. 1381 - 1396. © The Japan Institute of Heterocyclic Chemistry
Received, 1st March, 2007, Accepted, 10th April, 2007, Published online, 13th April, 2007. COM-07-11045

STEREOSELECTIVE SYNTHESIS OF POLYFUNCTIONALIZED AZIRIDINES

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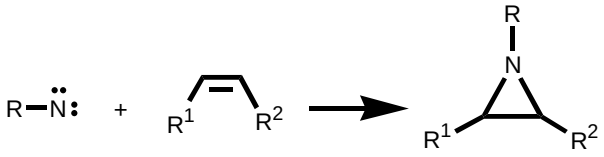
Abstract – 1,2,3-triHeterocycle-substituted aziridines were prepared by coupling of (α-chloroalkyl) oxazolinyllithium compounds with diheteroaryl imines. The trapping by different electrophiles of the corresponding aziridinyl anions, generated by treatment with strong bases, was investigated. The stereoselectivity of the synthesis and the functionalization reactions was studied highlighting the different stabilizing effects of the heterocycle substituents.

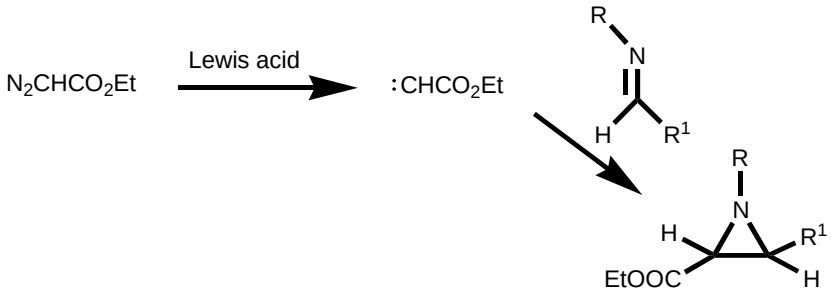
INTRODUCTION

In recent years, aziridines have been used extensively in organic synthesis as building blocks and synthetic intermediates.[1-3] Their importance originates from their ability to undergo ring-opening reaction with nucleophiles to afford a variety of multi-functional compounds.[4] For instance, the nucleophilic ring-opening reaction of substituted aziridines affords regioselectively functionalized α-, and β-amino acids.[5] Through ring expansion, aziridines could also give amido derivatives and oxazolines as protected forms of hydroxyl amino compounds.[6] Additionally, β-lactam antibiotics,[7] alkaloids,[8] amino sugars,[9] and chiral amines[10] could be obtained from this three-membered heterocycle. Enantiopure aziridines are also currently of interest as enzyme substrates and enzyme inhibitors.[11]

The development of efficient synthetic routes to aziridines is therefore a worthy target for the synthetic organic chemist, with the added requirement that any methods should also allow the stereoselective aziridine formation. Generally, aziridines are prepared from diazoacetates via ylide intermediates, olefins, and direct conversion of epoxides.[12] Another synthetic pattern extensively reported in literature and leading to aziridines is the nitrene addition to alkenes[13] (Scheme 1), and the carbene addition to imines,[14] (Scheme 2).

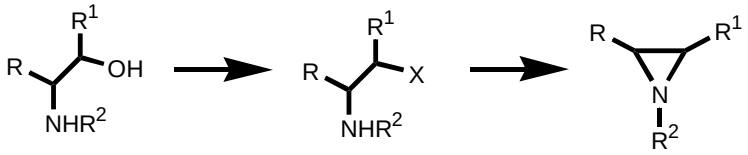


Scheme 1



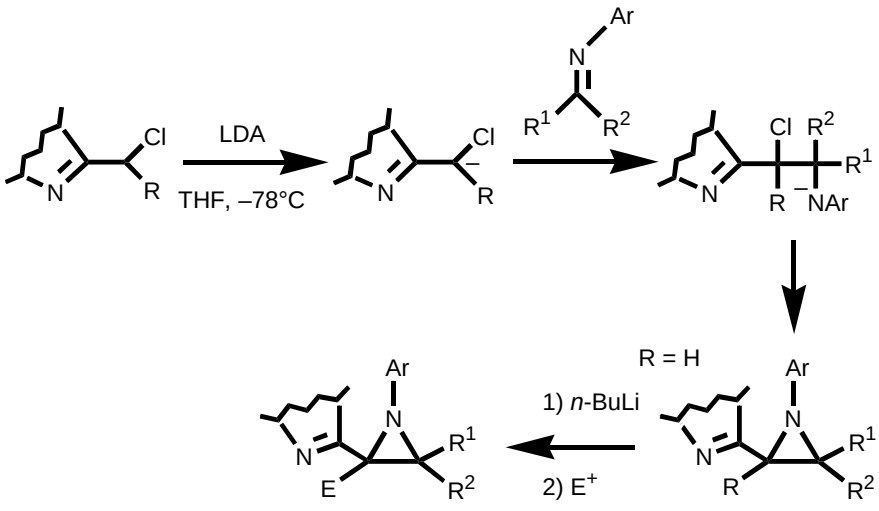
Scheme 2

Particularly interesting seems to be the intramolecular cyclization of β-amino alcohols[15] (Scheme 3).



Scheme 3

A variety of procedures for preparing chiral aziridines have been also extensively reviewed.[11] Moreover, a wide range of potential synthetic applications is possible using aziridines containing heterocyclic substituents, such as oxazoline, thiazole, benzothiazole, etc., which are able to free the masked carbonyl function.[16] Our research group has recently developed a methodology for a simple and diasteroselective synthesis of several heterosubstituted aziridines based on the Darzens reaction of lithiated (α-chloroalkyl)heterocycles with imines[17] (Scheme 4).



Scheme 4

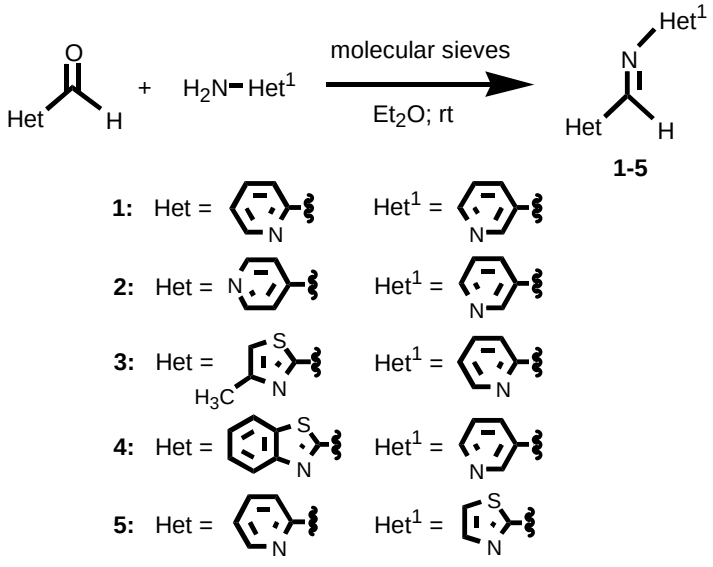
For instance, the high electron-withdrawing power of the heterocycles makes easier the ring deprotonation (with R = H), allowing a strong stabilization of the formed aziridinyl anion, which can be trapped by various electrophiles, to give more complex aziridines.[2,18,19] The reactions seem to proceed with retention of configuration or moderate stereoselectivity depending on the starting isomers.

With the goal of further exploring the chemistry of these molecules, we decided to investigate the synthesis of more complex 1,2,3-triheterocycle-substituted aziridines, through the coupling reaction of (α-chloroalkyl)oxazolinyllithium compounds with diheteroaryl imines. In this paper we also describe, as an obvious development of our previous work,[19] the capture by different electrophiles of the aziridinyl anion generated through the deprotonation of aziridines. Moreover, we have investigated the stereochemistry of these reactions, which provides new polyfunctionalized aziridines.

RESULTS AND DISCUSSION

Synthesis of 1,2,3-triheterocycle-substituted aziridines

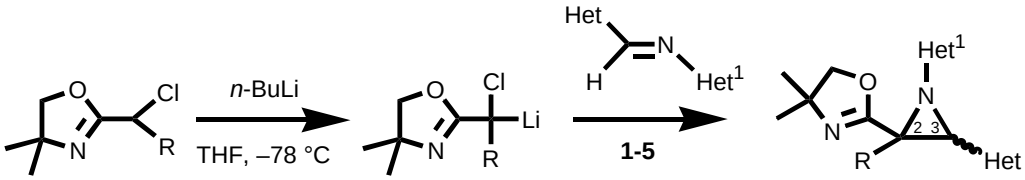
A series of heteroaryliden-heteroarylamines **1-5** (Scheme 5) were prepared following Taguchi's protocol,[20] by reaction of the appropriate heteroaryl carboxaldehyde with the corresponding heteroaryl amine in the presence of molecular sieves (Scheme 5).



Scheme 5

In order to perform the Darzens reaction, the α-chloroalkyl oxazolines **6** and **7** (Table 1), prepared according to known procedures,[21] were lithiated with *n*-BuLi in THF at –78 ° C, under nitrogen. The heteroaryliden-heteroarylamines **1-5** were added dropwise to the stirred solution of the oxazolinyllithium, to produce diastereoselectively the 1,2,3-triheterocycle-substituted aziridines **8-14** in satisfactory yields (35-80%). The obtained results are listed in Table 1.

Table 1. Synthesis of 1,2,3-triheterocycle-substituted aziridines **8-14**



6,7 **6', 7'** **8-14**

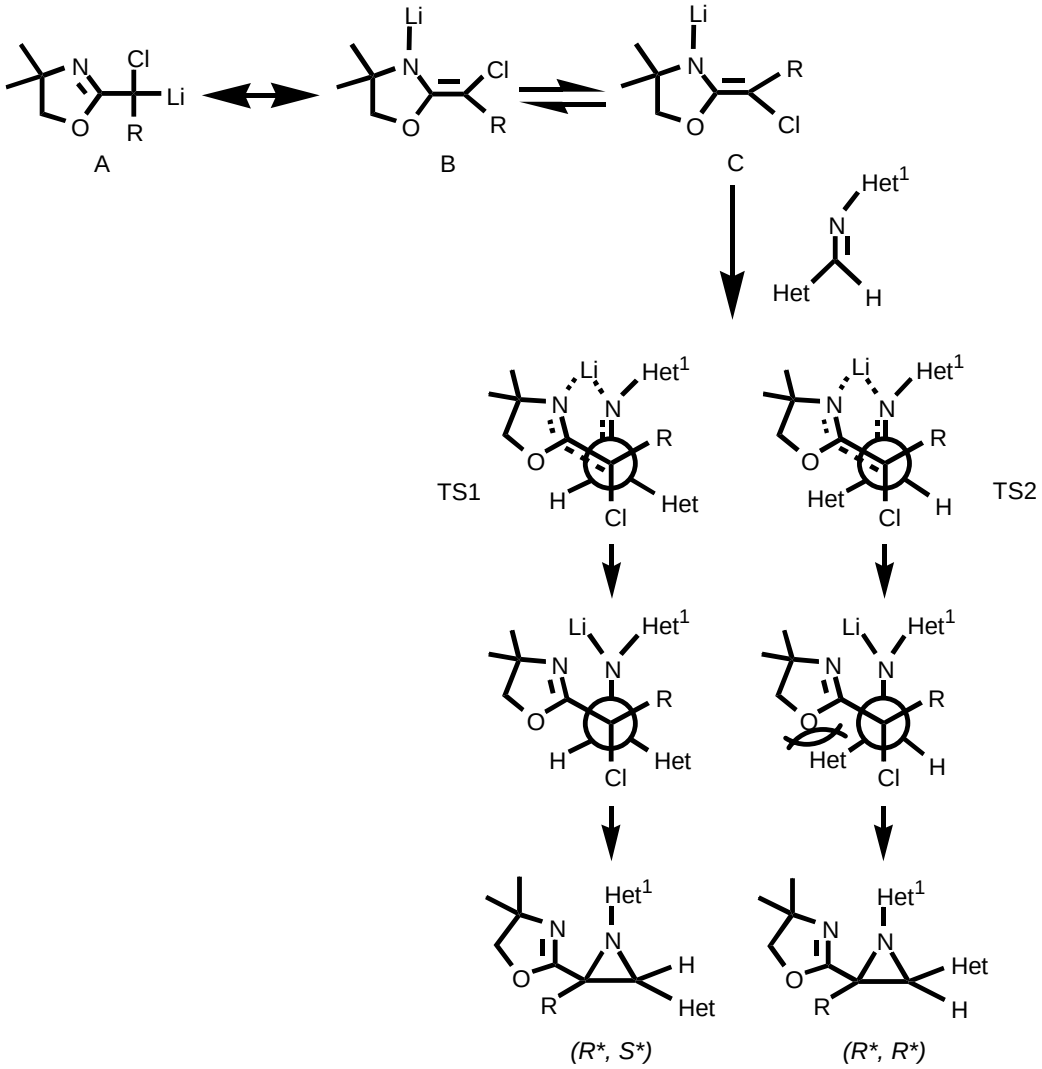
6 : R = CH_3 **7** : R = H

Entry	Chloroalkyl-oxazoline	Imine	Product	Total Yield[a] [%]	dr[b] *(R*, S*)/R*, R*)*
1	**6**	**1**	**8**	80	100/0
2	**6**	**2**	**9**	60	100/0
3	**6**	**3**	**10**	62	100/0
4	**6**	**4**	**11**	60	100/0
5	**6**	**5**	**12**	78	76/24
6	**7**	**2**	**13**	35	100/0
7	**7**	**1**	**14**	40	100/0

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

Surprisingly, all products were formed in a regiospecific manner, excepting the aziridine **12** (entry 5, Table 1) which was isolated in both diastereomers (*R*, S**) and (*R*, R*)* however with a strong predominance of the (*R*, S**) form. Contrarily to what we have found using imines bearing a phenyl at the nitrogen atom, where variable ratios of the two diastereomers were observed,[19] in this case, the reaction was stereoconvergent. The (*R*, S**)-aziridine was nearly always the only reaction product isolated, either starting from the α-chloroalkyl oxazoline **6** or **7**. The lower yields observed using the oxazoline **7** (entries 6 and 7, Table 1) are due to the ability of this latter to undergo readily the homocoupling reaction, together with the Darzens reaction. Instead, no homocoupling reaction was noticed in the case of the lithiated oxazoline **6**, which is sterically more hindered than **7**.

A possible explanation of the results here reported might be given by considering the structure of the oxazolinylalkyllithiums **6'**, **7'** and the rate-determining step in the reactions leading to the aziridines. There are spectroscopic evidences[22] that in heterocycle azines and azoles, as compounds **6'** and **7'**, a substantial proportion of the negative charge is delocalized on the aza-heterocycle system. Such propensity of the heterocycle groups to delocalize the negative charge is responsible for the double bond fixation at the exocyclic C=C bond in the anions **6'** and **7'**. These anions should exist as an equilibrium of the isomeric forms B and C which resonates with A (Scheme 6).



Scheme 6

The B/C ratio should be substantially shifted towards the stereomeric form C.[23] We presume that the carbanionic species C may discriminate between the two enantiotopic faces of the electrophilic imine, leading to the transition states TS1 and TS2, respectively. These latter are both stabilized by the intramolecular lithium chelation, but one of the two states should be energetically favoured in view of the steric interaction of the heterocycle groups (Scheme 6). For instance, TS1 which evolves to the (*R*, S**) aziridine is for evident steric reasons of lower energy than the TS2 transition state which would lead to the (*R*, R**) form. Moreover, the EWG linked at the nitrogen atom (Het[1]), could electronically influence the transition state formation and, consequently, the (*R*, S**)/(*R*, R**) ratios.

The (*R*, S**) and (*R*, R**) configurations of products deriving from **6** were assigned by the coupled ^{13}C NMR spectra: a very small or negligible $^{3}J_{CH_3\text{-}H}$ coupling constant (~0 Hz) corresponds to the (*R*, S**) configuration, while a larger $^{3}J_{CH_3\text{-}H}$ (~2.5-3.3 Hz) corresponds to the (*R*, R**) configuration.[24] For compounds deriving from **7**, the relative configurations were assigned on the basis of the ^{1}H NMR spectra through the $^{3}J_{H,H}$ coupling constants between the two protons on C2 and C3 (J_{trans} ~ 2-3 Hz; J_{cis} ~ 6-7

Hz).[25] Moreover, all the (*R*, S**) structures showed, in the ^{1}H NMR spectra, the oxazoline CH_2 signal as a double doublet with a chemical shift δ ~ 3.30-3.90 ppm (Δδ = 0.3-0.6 ppm, *J* ~ 8.0-8.2 Hz). The (*R*, R**) structures, instead, showed the oxazoline CH_2 signal as a multiplet with δ ~ 3.60-3.79 ppm.

Functionalization of 1,2,3-triheterocycle-substituted aziridines.

The known electron-withdrawing power of the three heterocycles linked to the aziridine ring should favour the generation of the aziridinyl anion, stabilizing it and influencing its reactivity in the coupling reaction with eletrophiles. The lithiation of aziridines (*R*, S**)-**14** and (*R*, S**)-**13**, showing two protons linked to the C2 and the C3, respectively, followed by the addition of deuterium oxide (D_2O) gave the 2-deuterated aziridines (*R*, R**)-**15** and (*R*, R**)-**16** as the only reaction products (entries 1 and 3, Table 2). The deprotonation by *n*-BuLi, in this case, seems to occur selectively at the C2 carbon bearing the oxazoline which shows a stronger electron-withdrawing effect compared to that of the pyridine linked to the C3 carbon atom and makes more acid the hydrogen linked to the C2. (*R*, S**)-**14** deprotonated and quenched with methyl iodide (CH_3I) afforded the 2-methylated aziridine (*R*, R**)-**8** (entry 2, Table 2). A complete inversion of configuration was noticed for all these three reactions. The deprotonation of the aziridines (*R*, S**)-**8**, (*R*, S**)-**12**, and (*R*, R**)-**12**, showing only one proton at the C3, and the quenching with different electrophiles, produced aziridines functionalized selectively at the C3 carbon atom. The generated aziridinyl anion trapped by D_2O inverted, partially, the configuration of the starting aziridine giving the 3-deuterated aziridines **17** and **20** in both the diastereomeric (*R*, S**) and (*R*, R**) forms (entries 4, 7, and 9, Table 2). The quenching of the lithiated (*R*, S**)-**8**, and (*R*, S**)-**12** with CH_3I or allyl bromide (entries 5, 6, and 8, Table 2) produced the compounds (*R*, R**)-**18**, (*R*, R**)-**19**, and (*R*, R**)-**21**, respectively, with predominant or complete inversion of configuration.

This behaviour seems to be totally new, since a high retention of configuration was previously reported with aziridines linking one or two heterocyles at the ring and a phenyl group to the nitrogen atom.[26,19] These results could be explained by the formation of an aziridinyllithium intermediate (I or II) which is stabilized by the intramolecular lithium chelation where the aziridine nitrogen plays a strategic role in the coordination of the aziridinyl anion (Figure 1). Thus, the electrophile attack may be prevalently driven on the opposite side with respect to the coordinated lithium, forming only one particular diastereoisomer and leading to the observed trend of inversion of configuration.

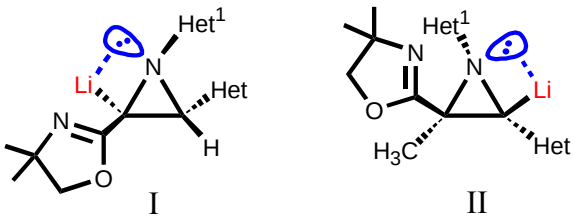
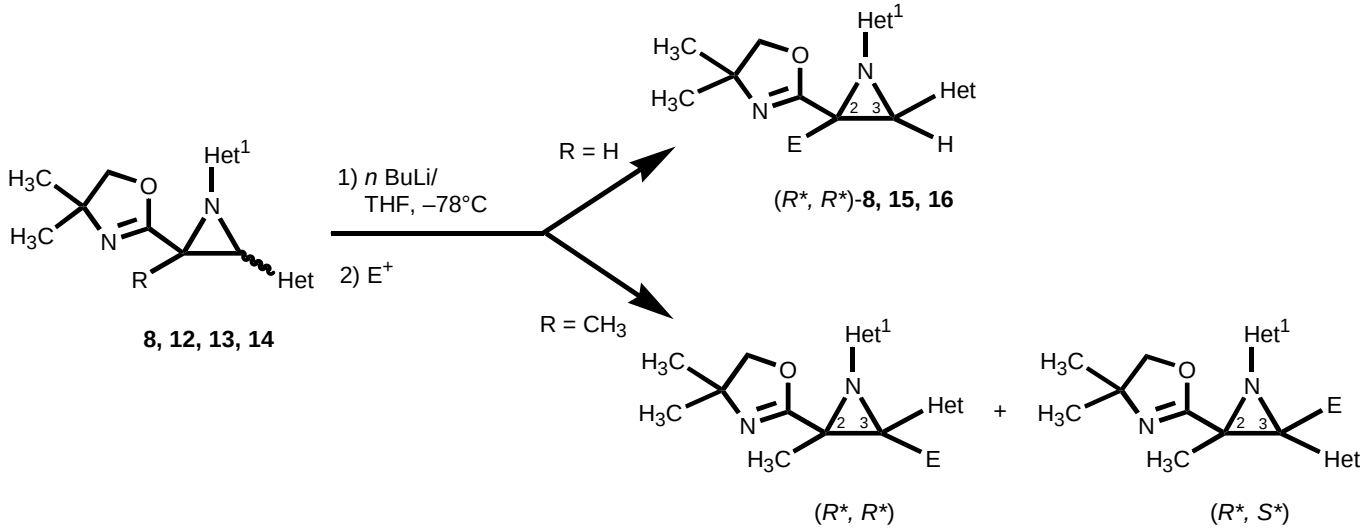


Figure 1

Table 2. Functionalization of 1,2,3-triheterocycle-substituted aziridines **8,12,13,14**



8, 12, 13, 14 **17-21**

Entry	Substrate	Electrophile	Product	Total Yield[a] [%]	dr[b] *(R*, S*)/R*, R*)*
1	*(R*, S*)*-**14**	D_2O	**15**	85	0/100
2	*(R*, S*)*-**14**	CH_3I	**8**	80	0/100
3	*(R*, S*)*-**13**	D_2O	**16**	90	0/100
4	*(R*, S*)*-**8**	D_2O	**17**	99	70/30
5	*(R*, S*)*-**8**	CH_3I	**18**	91	25/75
6	*(R*, S*)*-**8**		**19**	75	0/100
7	*(R*, S*)*-**12**	D_2O	**20**	80	72/28
8	*(R*, S*)*-**12**	CH_3I	**21**	75	0/100
9	*(R*, R*)*-**12**	D_2O	**20**	85	30/70

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

The structures of the deuterated aziridines **15**, **16**, **17** and **20** were established by ^{1}H NMR and by GC-MS data. For instance, in the ^{1}H NMR spectra the signal relative to the hydrogen substituted by a deuterium atom, almost disappeared. For compounds **15** and **16** the signal of the proton, linked to the opposite carbon of the aziridine ring, became a singlet with no chemical shift changes. Chemical shift displacements were observed, instead, for compounds inverting the configuration with respect to the starting aziridines. Moreover, deuterated compounds showed [M^+] mass values bigger of one unity with respect to those reported for the starting aziridines. The structures of the aziridines **18**, **19**, and **21** were assigned by NMR NOE and ^{1}H NMR experiments. The oxazoline CH_2 chemical shifts in the ^{1}H NMR

spectra of the (*R**, *R**) isomer showed a multiplet at about 3.60-3.79 ppm, while the same CH_2 signal in the (*R**, *S**) conformation showed a double doublet at about 3.30-3.90 ppm.

In conclusion, we reported the synthesis of new polyfunctionalized aziridines of synthetic potentiality considering also the additional ability of freeing the masked carbonyl group of some heteroaryl moieties linked to the aziridine ring. The stereoselectivity of the synthetic route and especially of the further functionalization reactions of these new aziridines makes the reported results extremely interesting. The oxazoline ring and the aziridine nitrogen provide an important contribution to the aziridine reactivity and to the regioselectivity, through the stabilizing effect on the corresponding aziridinyl anion thereof generated. Further works are going on in our laboratory on aziridines having three heteroaryls as substituents, and without oxazoline moiety. The preliminary results obtained and not yet published seem to confirm the results reported in this paper.

EXPERIMENTAL

General Remarks: *n*-BuLi was a commercial solution in hexanes (Aldrich) and was titrated with *N*-pivaloyl-*o*-toluidine prior to use.[27] THF, 4-formylmorpholine, 2-pyridinecarboxaldehyde, 4-pyridinecarboxaldehyde, 2-aminothiazole, 2-aminopyridine, 3-aminopyridine, 4-methyl-thiazole, 2-aminothiophenol, glycolic acid, D_2O, methyl iodide and all other chemicals were of commercial grade (Aldrich) and were used without further purification. Allyl bromide (Aldrich) was purified by distillation prior to use. The (α-chloromethyl)oxazoline **6** and the (α-chloroethyl)oxazoline **7** were prepared by chlorination[21] of the commercial 2-methyl- and 2-ethyl-2-oxazolines (Aldrich). The heteroarylidene-heteroarylamines **1**-**5** were prepared by coupling reaction of heteroarylamines with the appropriate heteroaryl carboxaldehydes by Taguchi's procedure.[20] Among them, the amines **3** and **4** were previously prepared and fully characterized by us.[28] 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 FT-IR spectrophotometer Digilab Scimitar Series FTS 2000. GC-MS analyses were performed on an Agilent Technologies 6850 series II gas chromatograph (5% phenyl-polymethylsiloxane capillary column, 30 m, 0.25 mm i.d.), fitted with a 5973 Network 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 ionization source. MS(+) spectra were acquired by direct infusion (5 μL/min) of a solution containing the appropriate sample (10 pmol/μL), 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. Elemental analyses were performed on a Carlo Erba C, H, N analyzer. 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 μm) with use of the following mixtures as eluents: petroleum ether/diethyl ether (Et_2O), petroleum ether/EtOAc and petroleum ether/Et_2O/MeOH. All reactions involving air-sensitive reagents were performed under nitrogen, in oven-dried glassware using syringe/septum cap techniques.

***N*-(Pyridin-2-ylmethylene)pyridin-3-amine (1).** Yield: 179 mg (98%), yellow oil. ^{1}H NMR ($CDCl_3$): δ 7.36 (dd, *J* = 5.2, 8.0 Hz, 1 H), 7.39-7.42 (m, 1 H), 7.58-7.61 (m, 1 H), 7.83 (t, *J* = 7.7 Hz, 1 H), 8.21 (d, *J* = 7.7 Hz, 1 H), 8.52 (d, *J* = 4.7 Hz, 1 H), 8.57 (d, *J* = 2.0 Hz, 1 H), 8.62 (s, 1 H) 8.74 (d, *J* = 4.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 122.1, 123.7, 125.5, 127.7, 136.7, 143.0, 146.8, 147.8, 149.8, 154.0, 162.4. GC-MS (70 eV) *m/z* (%): 183 (91) [M^+], 182 (100), 155 (86), 130 (21), 105 (25), 78 (70). IR ($CHCl_3$): 3059, 2984, 1632, 1588, 1476, 1438, 1418 cm^{-1}. HRMS calcd. for $C_{11}H_9N_3$ 183.07977; found 183.07967.

N*-(Pyridin-4-ylmethylene)pyridin-3-amine (2).** Yield: 174 mg (95%), yellow solid, m.p. 46-48 ° C (*n*-hexane). ^{1}H NMR ($CDCl_3$): δ 7.36 (dd, *J* = 4.8, 8.3 Hz, 1 H), 7.55-7.58 (m, 1 H), 7.77 (d, *J* = 6.0 Hz, 2 H), 8.48 (s, 1 H), 8.52-8.55 (m, 2 H), 8.79 (d, *J* = 6.0 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 122.2, 123.7, 127.8, 142.1, 142.5, 146.7, 148.1, 150.7, 159.7. GC-MS (70 eV) *m/z* (%): 183 (100) [M^+], 182 (84), 155 (10), 105 (42), 78 (74). IR ($CHCl_3$): 3059, 2986, 1632, 1600, 1560, 1476, 1417, 1320, 1229, 1185 cm^{-1}. ***Anal. Calcd for $C_{11}H_9N_3$: C 72.11, H 4.95, N 22.94. Found C 72.01, H 4.90, N 22.90.

N*-(Pyridin-2-ylmethylene)thiazol-2-amine (5)** Yield: 151 mg (80%), yellow solid, m.p. 72-73 ° C (*n*-hexane). ^{1}H NMR ($CDCl_3$): δ 7.29 (d, *J* = 3.4 Hz, 1 H), 7.39-7.43 (m, 1 H), 7.74 (d, *J* = 3.4 Hz, 1 H), 7.83 (t, *J* = 6.8 Hz, 1 H), 8.26 (d, *J* = 7.8 Hz, 1 H), 8.75 (d, *J* = 4.3 Hz, 1 H), 9.08 (s, 1 H). ^{13}C NMR ($CDCl_3$): δ 119.0, 122.9, 125.8, 136.6, 141.8, 150.0, 153.4, 163.6, 172.0. GC-MS (70 eV) *m/z* (%): 189 (100) [M^+], 188 (55), 162 (35), 105 (24), 78 (20). IR ($CHCl_3$): 3059, 2994, 1625, 1609, 1499, 1470, 1417, 1215, 1138 cm^{-1}. ***Anal. Calcd for $C_9H_7N_3S$: C 57.12, H 3.73, N 22.20. Found C 57.02, H 3.78, N 22.17.

General procedure for the preparation of 1,2,3-triheterocycle-substituted aziridines 8-14. *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 compound **1-5** (1.3 mmol) and **6** or **7** (1.0 mmol) in THF (10 mL). After 20 min. the resulting mixture was allowed to warm slowly to rt and then, after 3 h, quenched with H_2O. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O or petroleum ether/EtOAc) to afford the pure products, **8-14**, total yields: 35-80%.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-methyl-1-pyridin-3-ylaziridin-2-yl]pyridine (8). (*R*, S**)-**8** yield: 246 mg (80%), oil. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 3 H), 1.20 (s, 3 H), 1.45 (s, 3 H), 3.37

(d, *J* = 8.1 Hz, 1 H), 3.75 (d, *J* = 8.1 Hz, 1 H), 4.38 (s, 1 H), 7.16 (dd, *J* = 4.7, 8.2 Hz, 1 H), 7.25-7.30 (m, 2 H), 7.49 (d, *J* = 7.8 Hz, 1 H), 7.70-7.49 (dt, *J* = 1.7, 7.8 Hz, 1 H), 8.25 (dd, *J* = 1.3, 4.7 Hz, 1 H), 8.32 (d, *J* = 2.6 Hz, 1 H), 8.65 (d, *J* = 4.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 16.1, 27.9, 28.4, 45.6, 50.8, 67.6, 78.8, 122.2, 122.7, 123.0, 126.6, 136.4, 142.1, 143.8, 145.8, 149.5, 155.5, 161.5. GC-MS (70 eV) *m/z* (%): 308 (17) [M^+], 293 (64), 230 (35), 210 (64), 209 (12), 119 (100). IR (film): 3054, 2969, 2932, 2870, 1654, 1590, 1477, 1423, 1242, 1125, 803 cm^{-1}. HRMS calcd. for $C_{18}H_{20}N_4O$ 308.16390; found 308.16378.

3-[2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-2-methyl-3-pyridin-4-ylaziridin-1-yl]pyridine (9). (*R*, S**)-**9** Yield: 185 mg (60%), oil. ^{1}H NMR ($CDCl_3$): δ 0.96 (s, 3 H), 1.21 (s, 3 H), 1.40 (s, 3 H), 3.48 (d, *J* = 8.2 Hz, 1 H), 3.78 (d, *J* = 8.2 Hz, 1 H), 4.22 (s, 1 H), 7.17 (dd, *J* = 4.47, 9.0 Hz, 1 H), 7.25-7.28 (m, 1 H), 7.40 (d, *J* = 5.7 Hz, 2 H), 8.27 (dd, *J* = 1.0, 4.6 Hz, 1 H), 8.30 (d, *J* = 2.5 Hz, 1 H), 8.60 (d, *J* = 5.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 16.0, 27.9, 28.3, 45.9, 47.8, 67.5, 79.1, 122.8, 123.1, 126.8, 142.2, 144.1, 144.4, 145.5, 149.8, 161.3. GC-MS (70 eV) *m/z* (%): 308 (45) [M^+], 253 (55), 230 (33), 119 (100), 78 (61). IR (film): 3032, 2969, 2931, 1655, 1602, 1583, 1423, 1125 cm^{-1}. HRMS calcd. for $C_{18}H_{20}N_4O$ 308.16390; found 308.16377.

2-[2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-2-methyl-3-(4-methyl-thiazol-2-yl)aziridin-1-yl]pyridine (10). (*R*, S**)-**10** Yield: 203 mg (62%), oil. ^{1}H NMR ($CDCl_3$): δ 1.10 (s, 3 H), 1.20 (s, 3 H), 1.63 (s, 3 H), 2.48 (d, *J* = 0.6 Hz, 3 H), 3.32 (d, *J* = 8.1 Hz, 1 H), 3.62 (d, *J* = 8.1 Hz, 1 H), 4.69 (s, 1 H), 6.62-6.65 (m, 2 H), 6.85-6.94 (m, 1 H), 7.55 (dt, *J* = 1.9, 8.2 Hz, 1 H), 8.29 (d, *J* = 4.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 16.3, 17.1, 27.8, 28.4, 46.7, 56.0, 67.6, 79.1, 113.8, 114.5, 118.6, 137.3, 148.3, 153.6, 160.7, 161.6, 166.2. GC-MS (70 eV) *m/z* (%): 328 (9) [M^+], 313 (3), 216 (93), 144 (100), 78 (22). IR (film): 3082, 2969, 2928, 2870, 1656, 1590, 1469, 1431, 1122, 974 cm^{-1}. HRMS calcd. for $C_{17}H_{20}N_4OS$ 328.13600; found 328.13620.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-methyl-1-pyridin-3-ylaziridin-2-yl]-1,3-benzothiazole (11). (*R*, S**)-**11** Yield: 218 mg (60%), oil. ^{1}H NMR ($CDCl_3$): δ 1.05 (s, 3 H), 1.20 (s, 3 H), 1.69 (s, 3 H), 3.42 (d, *J* = 8.2 Hz, 1 H), 3.78 (d, *J* = 8.2 Hz, 1 H), 4.64 (s, 1 H), 7.19 (dd, *J* = 4.6, 8.2 Hz, 1 H), 7.32 (m, 1 H), 7.43 (t, *J* = 7.0 Hz, 1 H), 7.52 (t, *J* = 8.2 Hz, 1 H), 7.91 (d, *J* = 8.0 Hz, 1 H), 8.06 (d, *J* = 8.0 Hz, 1 H), 8.30 (d, *J* = 4.7 Hz, 1 H), 8.36 (d, *J* = 2.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 16.4, 27.9, 28.3, 48.0, 47.2, 67.7, 79.1, 121.7, 123.0, 123.2, 125.3, 126.3, 126.8, 134.8, 141.9, 144.4, 144.7, 153.9, 160.6, 167.5. GC-MS (70 eV) *m/z* (%): 364 (100) [M^+], 349 (15), 265 (22), 148 (40), 119 (50). IR (film): 3060, 2965, 2929, 1655, 1458, 1425, 1122, 761 cm^{-1}. HRMS calcd. for $C_{20}H_{20}N_4OS$ 364.13600; found 364.13615.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-methyl-1-thiazol-2-yl-aziridin-2-yl]pyridine (12). Separable mixture of two diastereomers in a ratio of 76/24. Overall yield 78%. (*R*, S**)-**12** Yield: 185 mg (59%), oil. ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 3 H), 1.26 (s, 3 H), 1.46 (s, 3 H), 3.53 (d, *J* = 8.0 Hz, 1 H), 3.85 (d, *J* = 8.0 Hz, 1 H), 4.75 (s, 1 H), 6.85 (d, *J* = 3.6 Hz, 1 H), 7.24-7.26 (m, 1 H), 7.32 (d, *J* = 3.6 Hz, 1 H),

7.51 (d, *J* = 7.8 Hz, 1 H), 7.69-7.63 (m, 1 H), 8.63 (d, *J* = 4.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 15.7, 27.9, 28.3, 48.2, 52.9, 67.6, 79.4, 113.5, 122.4, 122.8, 136.5, 139.2, 149.4, 154.7, 161.2, 172.1. GC-MS (70 eV) *m/z* (%): 314 (60) [M^+], 299 (12), 215 (100), 99 (25). IR (film): 3079, 2967, 2930, 2870, 1653, 1504, 1455, 1151 cm^{-1}. HRMS calcd. for $C_{16}H_{18}N_4OS$ 314.12034; found 314.12040. (*R*, R**)-**12** Yield: 60 mg (19%), oil. ^{1}H NMR ($CDCl_3$): δ 0.96 (s, 3 H), 1.11 (s, 3 H), 1.60 (s, 3 H), 3.69-3.73 (m, 2 H), 4.13 (s, 1 H), 6.94 (d, *J* = 3.7 Hz, 1 H), 7.18-7.21 (m, 1 H), 7.38 (d, *J* = 3.7 Hz, 1 H), 7.36 (d, *J* = 7.9 Hz, 1 H), 7.62-7.66 (m, 1 H), 8.56 (d, *J* = 4.1 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 16.9, 28.0, 48.8, 54.7, 67.3, 79.4, 114.7, 122.5, 122.7, 136.1, 139.6, 148.9, 154.5, 161.7, 170.8. GC-MS (70 eV) *m/z* (%): 314 (19) [M^+], 299 (17), 215 (100), 99 (28). IR ($CHCl_3$): 3061, 2968, 2930, 2856, 1671, 1505, 1455, 1154 cm^{-1}. HRMS calcd. for $C_{16}H_{18}N_4OS$ 314.12034; found 314.12024.

3-[2-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-pyridin-4-ylaziridin-1-yl]pyridine (13). (*R**, *S**)-**13** Yield: 103 mg (35%), oil. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 3 H), 1.26 (s, 3 H), 3.35 (d, *J* = 2.6 Hz, 1 H), 3.61 (d, *J* = 8.0 Hz, 1 H), 3.86 (d, *J* = 8.0 Hz, 1 H), 3.87 (d, *J* = 2.6 Hz, 1 H), 7.16-7.19 (m, 1 H), 7.21-7.25 (m, 1 H), 7.31 (d, *J* = 5.8 Hz, 2 H), 8.28 (d, *J* = 4.6 Hz, 1 H), 8.31 (d, *J* = 2.6 Hz, 1 H), 8.60 (d, *J* = 5.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 28.0, 28.3, 42.9, 43.6, 67.7, 79.3, 121.6, 123.3, 127.3, 142.4, 144.4, 144.6, 145.3, 150.0, 158.7. GC-MS (70 eV) *m/z* (%): 294 (38) [M^+], 239 (14), 216 (37), 105 (100), 78 (51). IR ($CHCl_3$): 3038, 2969, 2929, 2855, 1660, 1604, 1480, 1425, 1190 cm^{-1}. HRMS calcd. for $C_{17}H_{18}N_4O$ 294.14824; found 294.14813.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-pyridin-3-ylaziridin-2-yl]pyridine (14). (*R**, *S**)-**14** Yield: 118 mg (40%), oil. ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 3 H), 1.27 (s, 3 H), 3.65 (d, *J* = 8.1 Hz, 1 H), 3.70 (d, *J* = 2.6 Hz, 1 H), 3.87 (d, *J* = 8.1 Hz, 1 H), 4.06 (d, *J* = 2.6 Hz, 1 H), 7.13 (dd, *J* = 4.7, 8.1 Hz, 1 H), 7.21 (dd, *J* = 4.7, 7.4 Hz, 1 H), 7.26-7.33 (m, 1 H), 7.42 (d, *J* = 7.8 Hz, 1 H), 7.68 (t, *J* = 7.8 Hz, 1 H), 8.22 (d, *J* = 4.7 Hz, 1 H), 8.28 (d, *J* = 2.25 Hz, 1 H), 8.52 (d, *J* = 4.5 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 28.1, 28.3, 41.3, 46.0, 67.6, 79.2, 122.1, 123.0, 123.1, 127.4, 136.7, 142.7, 143.9, 145.0, 149.6, 154.7, 159.7. GC-MS (70 eV) *m/z* (%): 294 (10) [M^+], 293 (25), 216 (77), 196 (100), 105 (30), 78 (51). IR ($CHCl_3$): 3056, 2969, 2932, 2872, 1660, 1592, 1478, 1425, 1265 cm^{-1}. HRMS calcd. for $C_{17}H_{18}N_4O$ 294.14824; found 294.14810.

General procedure for the functionalization of aziridines 8, 12, 13 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 (10mL). The resulting mixture was stirred at –78 ° C for 20 min., and the corresponding electrophile (1.5 mmol) was then added. The mixture was allowed to warm to rt and quenched with H_2O. The aqueous layer was extracted with Et_2O (3 x 20 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography (silica gel, petroleum ether/Et_2O/MeOH, 2.5:7:0.5) to afford the pure

polyfunctionalized aziridines **8,15** (yields: 80%, 85%), **16** (yield: 90%), **17-19** (yields: 75-99%), and **20,21** (yields: 75%, 85%).

2-[3-Deutero-3-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-pyridin-3-ylaziridin-2-yl]pyridine (15). (*R*, R**)-**15** Yield: 251 mg (85%), oil. ^{1}H NMR ($CDCl_3$): δ 0.99 (s, 3 H), 1.19 (s, 3 H), 3.74-3.79 (m, 3 H), 7.13-7.25 (m, 2 H), 7.42 (dd, *J* = 1.5, 8.1 Hz, 1 H), 7.63 (d, *J* = 7.7Hz, 1 H), 7.69 (td, *J* = 1.5, 7.7 Hz, 1 H), 8.32 (d, *J* = 4.6 Hz, 1 H), 8.46 (s, 1 H), 8.58 (d, *J* = 4.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 28.0, 28.1, 41.2, 47.6, 67.3, 79.4, 122.6, 122.9, 123.6, 127.3, 136.1, 142.5, 144.9, 148.3, 149.1, 154.4, 159.0. GC-MS (70 eV) *m/z* (%): 295 (10) [M^+], 294 (25), 293 (26), 217 (50), 216 (75), 197 (71), 196 (100), 78 (55). IR ($CHCl_3$): 3061, 2974, 2932, 2872, 1660, 1586, 1478, 1426 cm^{-1}. HRMS calcd. for $C_{17}H_{17}DN_4O$ 295.15451; found 295.15440.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-methyl-1-pyridin-3-ylaziridin-2-yl]pyridine (8). (*R*, R**)-**8** Yield: 246 mg (80%), oil. ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3 H), 1.14 (s, 3 H), 1.49 (s, 3 H), 3.70-3.74 (m, 3 H), 7.18-7.24 (m, 2 H), 7.34 (d, *J* = 8.0 Hz, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.65 (t, *J* = 7.2 Hz, 1 H), 8.31 (d, *J* = 4.6 Hz, 1 H), 8.37 (d, *J* = 2.5 Hz, 1 H), 8.59 (d, *J* = 4.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.0, 29.6, 30.3, 46.0, 53.0, 67.2, 79.4, 122.0, 122.7, 123.4, 127.5, 136.1, 140.9, 142.5, 144.3, 148.9, 155.1, 162.3. GC-MS (70 eV) *m/z* (%): 308 (10) [M^+], 293 (40), 230 (25), 210 (49), 119 (100), 78 (33). IR ($CHCl_3$): 3059, 2969, 2930, 1667, 1586, 1478, 1420, 1384, 1103 cm^{-1}. HRMS calcd. for $C_{18}H_{20}N_4O$: 308.16390; found 308.16382.

3-[2-Deutero-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-pyridin-4-ylaziridin-1-yl]pyridine (16). (*R*, R**)-**16** Yield: 265 mg (90%), oil. ^{1}H NMR ($CDCl_3$): δ 1.01 (s, 3 H), 1.15 (s, 3 H), 3.73 (d, *J* = 8.2 Hz, 1 H), 3.77 (d, *J* = 8.2 Hz, 1 H), 4.17 (s, 1 H), 7.21-7.25 (m, 1 H), 7.39 (d, *J* = 8.1 Hz, 1 H), 7.45 (d, *J* = 5.9 Hz, 2 H), 8.43 (d, *J* = 2.4 Hz, 1 H), 8.55 (d, *J* = 5.9 Hz, 1 H), 8.60 (dd, *J* = 2.4, 5.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ 28.1, 45.9, 57.7, 69.2, 78.8, 122.1, 123.2, 123.5, 142.2, 143.5, 144.1, 145.5, 149.7, 158.7. GC-MS (70 eV) *m/z* (%): 295 (20) [M^+], 161 (40), 106 (90), 105 (100), 78 (60). IR ($CHCl_3$): 3037, 2969, 2931, 2854, 1664, 1603, 1480, 1426, 1189 cm^{-1}. HRMS calcd. for $C_{17}H_{17}DN_4O$ 295.15451; found 295.15444.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-methyl-1-pyridin-3-yl-2-deuteroaziridin-2-yl]pyridine (17). Separable mixture of two diastereomers in a ratio of 70/30. Overall yield 99%. (*R*, S**)-**17** Yield: mg 213 (69%), oil. The ^{1}H NMR, the ^{13}C NMR and the IR data are the same of those reported for (*R**, *S**)-**8**. In the ^{1}H NMR spectrum the singlet at 4.38 ppm almost disappeared. The GC-MS data showed a [M^+] mass value greater by one unity than those reported for the starting (*R**, *S**)-**8**. HRMS calcd. for $C_{18}H_{19}DN_4O$ 309.17017; found 309.17052. (*R*, R**)-**17** Yield: 93 mg (30%), oil. ^{1}H NMR ($CDCl_3$): δ 0.97 (s, 3 H), 1.15 (s, 3 H), 1.49 (s, 3 H), 3.74-3.76 (m, 2 H), 7.20-7.25 (m, 2 H), 7.29-7.36 (m, 1 H), 7.54 (d, *J* = 8.0 Hz, 1 H), 7.66 (td, *J* = 1.6, 7.6 Hz, 1 H), 8.31-8.32 (m, 1 H), 8.38 (d, *J* = 2.0 Hz, 1

H), 8.59 (d, *J* = 4.9 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 15.3, 29.5, 29.6, 50.0, 55.9, 69.2, 78.9, 122.7, 122.8, 123.7, 127.7, 136.5, 141.7, 141.8, 142.5, 149.7, 167.0, 168.7. GC-MS (70 eV) *m/z* (%): 309 (59) [M^+], 294 (34), 231 (34), 211 (56), 119 (100), 78 (80). IR ($CHCl_3$): 3059, 2968, 2929, 1670, 1583, 1476, 1420, 1381, 1101 cm^{-1}. HRMS calcd. for $C_{18}H_{19}DN_4O$: 309.17017; found 309.17001.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-2,3-dimethyl-1-pyridin-3-ylaziridin-2-yl]pyridine (18). Separable mixture of two diastereomers in a ratio of 25/75. Overall yield 91%. (*R*, S**)-**18** Yield: 74 mg (23%), oil. ^{1}H NMR ($CDCl_3$): δ 1.22 (s, 3 H), 1.25 (s, 3 H), 1.32 (s, 3 H), 1.82 (s, 3 H), 3.76 (d, *J* = 8.1 Hz, 1 H), 3.83 (d, *J* = 8.1 Hz, 1 H), 7.14-7.26 (m, 3 H), 7.48 (d, *J* = 7.8 Hz, 1 H), 7.69 (t, *J* = 7.8 Hz, 1 H), 8.20-8.23 (m, 2 H), 8.62 (d, *J* = 4,0 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 14.1, 16.2, 28.2, 28.3, 47.1, 54.2, 67.5, 79.6, 122.2, 122.8, 123.6, 126.4, 136.6, 141.4, 141.5, 142.6, 149.2, 161.1, 162.2. GC-MS (70 eV) *m/z* (%): 322 (76) [M^+], 307 (91), 224 (78), 198 (100), 106(80), 78 (88). IR ($CHCl_3$): 3039, 2968, 2930, 2856, 1664, 1589, 1482 cm^{-1}. HRMS calcd. for $C_{19}H_{22}N_4O$ 322.17956; found 322.17949. (R*, R*)-**18** Yield: 219 mg (68%), oil. ^{1}H NMR ($CDCl_3$): δ 0.74 (s, 3 H), 1.07 (s, 3 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 3.60-3.66 (m, 2 H), 7.16-7.20 (m, 1 H), 7.22-7.24 (m, 2 H), 7.63-7.65 (m, 2 H), 8.27 (d, *J* = 2.8 Hz, 2 H), 8.57 (d, *J* = 4.7 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 12.9, 14.7, 27.7, 27.8, 46.9, 53.0, 66.7, 79.3, 122.1, 123.4, 127.2, 136.2, 141.6, 142.1, 142.9, 148.6, 149.5, 160.2, 163.7. GC-MS (70 eV) *m/z* (%): 322 (26) [M^+], 307 (31), 224 (40), 223 (100), 196 (31), 104 (22), 78 (43). IR ($CHCl_3$): 3058, 2969, 2929, 1669, 1584, 1477, 1422, 1384, 1105 cm^{-1}. HRMS calcd. for $C_{19}H_{22}N_4O$ 322.17956; found 322.17960.

2-[2-Allyl-3-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-methyl-1-pyridin-3-ylaziridin-2-yl]pyridine (19). (*R*, R**)-**19** Yield: 261 mg (75%), oil. ^{1}H NMR ($CDCl_3$): δ 0.74 (s, 3 H), 1.09 (s, 3 H), 1.63 (s, 3 H), 2.46 (dd, *J* = 7.4, 15.3 Hz, 1 H), 2.97 (dd, *J* = 6.6, 15.3 Hz, 1 H), 3.61 (d, *J* = 8.0 Hz, 1 H), 3.67 (d, *J* = 8.0 Hz, 1 H), 4.98-5.06 (m, 2 H), 5.74-5.84 (m, 1 H), 7.16-7.33 (m, 3 H), 7.59 (d, *J* = 7.8 Hz, 1 H), 7.65 (t, *J* = 7.8 Hz, 1 H), 8.26 (d, *J* = 4.6 Hz, 1 H), 8.34 (d, *J* = 2,5 Hz, 1 H), 8.59 (d, *J* = 4.6 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 12.8, 27.7, 27.9, 33.6, 46.2, 55.4, 66.7, 79.5, 118.6, 122.1, 123.4, 123.6, 127.7, 132.9, 136.1, 141.5, 142.6, 142.9, 148.6, 158.7, 163.8. GC-MS (70 eV) *m/z* (%): 348 (6) [M^+], 333 (12), 255 (100), 234 (12), 78 (20). IR ($CHCl_3$): 3061, 2967, 2930, 1671, 1585, 1480, 1424, 1285, 1091 cm^{-1}. HRMS calcd. for $C_{21}H_{24}N_4O$ 348.19522; found 348.19534.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-3-methyl-1-thiazol-2-yl-2-deuteroaziridin-2-yl]pyridine (20). Separable mixture of two diastereomers in a ratio of 72/28 (entry 7, Table 2) or 30/70 (entry 9, Table 2). Overall yield 80 or 85%. (*R*, S**)-**20** Yield: mg 183 or 82 (58 or 26%), oil. The ^{1}H NMR, the ^{13}C NMR and the IR data are the same of those reported for (*R**, *S**)-**12**. In the ^{1}H NMR spectrum the singlet at 4.75 ppm almost disappeared. The GC-MS data showed a [M^+], mass value greater by one unity than those reported for the starting (*R**, *S**)-**12**. HRMS calcd. for $C_{16}H_{17}DN_4OS$ 315.12661; found 315.12695. (*R*, R**)-**20** Yield: 69 mg or 186 mg (22 or 59%), oil. The ^{1}H NMR, the ^{13}C NMR and the IR

data are the same of those reported for (*R**, *R**)-**12**. In the ^{1}H NMR spectrum the singlet at 4.13 ppm almost disappeared. The GC-MS data showed a [M^+], mass value greater by one unity than those reported for the starting (*R**, *R**)-**12**. HRMS calcd. for $C_{16}H_{17}DN_4OS$ 315.12661; found 315.12650.

2-[3-(4,4-Dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-2,3-dimethyl-1-thiazol-2-yl-aziridin-2-yl]pyridine (21). (*R**, *R**)-**21** Yield: 246 mg (75%), oil. ^{1}H NMR ($CDCl_3$): δ 0.73 (s, 3 H), 1.04 (s, 3 H), 1.74 (s.3 H), 1.77 (s,3 H), 3.61 (s, 2 H), 7.29 (d, *J* = 3.4 Hz, 1 H), 7.14-7.18 (m, 1 H), 7.61-7.66 (m, 2 H), 7.24 (d, *J* = 3.4 Hz, 1 H), 8.54 (dd, *J* = 1.1, 5.8 Hz, 1 H). ^{13}C NMR ($CDCl_3$): δ 12.1, 15.4, 27.6, 27.8, 49.6, 55.8, 66.8, 79.4, 122.2, 122.6, 127.3, 136.3, 136.7, 148.8, 159.5, 162.9, 165.8. GC-MS (70 eV) *m/z* (%): 328 (35) [M^+], 250 (5), 229 (83), 216 (100), 78 (21). IR ($CHCl_3$): 3062, 2971, 2931, 2859, 1674, 1593, 1519, 1476, 1151 cm^{-1}. HRMS calc. for $C_{17}H_{20}N_4OS$: 328.13600. Found 328.13610.

ACKNOWLEDGEMENTS

This work was carried out under the framework of the National Project 'Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni' supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR, Rome). We would like to thank also the University of Lecce and the C.I.N.M.P.I.S. (Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi) for the financial support.

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