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Synthesis of chiral 1-(2-aminoalkyl)aziridines *via* a self-opening reaction of aziridine

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Dedicated to Professor Jacek Młochowski on the occasion of his 80th anniversary

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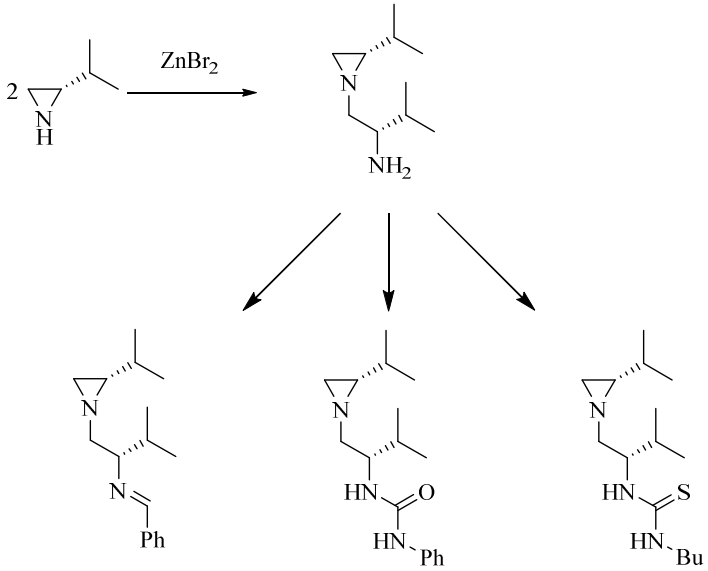
Abstract

A novel approach to the synthesis of optically pure 1-(2-aminoalkyl)aziridines *via* a nucleophilic ring-opening reaction of aziridine is presented. The reaction takes place under mild conditions in the presence of $ZnBr_2$ with moderate chemical yields. The formation of 1-(2-aminoalkyl)aziridines, starting from optically pure NH-aziridines, occurs selectively, leading to a single diastereoisomer.



Keywords: Aziridine, diamine, aminoalkylaziridine, ring-opening of aziridine

Introduction

Various types of 1,2-diamines (primary, secondary, tertiary, cyclic, non-cyclic) play a fundamental role in several fields of chemistry, biology and medicine. These compounds range from natural products, including those which perform essential metabolic functions within the human body, to synthetic (unnatural) products, some of which have become important medicinal agents in the treatment of a variety of diseases. Numerous compounds containing the chiral 1,2-diamine motif are applied in many drugs (e.g. Oxaliplatin and other platinum-based drugs[1-2]). Especially 1,2-diamines containing one tetra-substituted center and an unsubstituted methylene group CH_2(N-CR_2-CH_2N) are highly relevant privileged moieties because of their presence in the structures of compounds exhibiting pharmacological properties, such as in antitumor, anti-infective, anti-inflammatory, antidiabetic and cardiovascular agents, as well as in enzyme inhibitors and immune agents. The homochiral tetra-substituted centers are one of the keys to their biological role. Because of the importance of these structures, the search for synthetic methods able to produce them in an optically pure form has become extremely important.

Moreover, such compounds play a special role in asymmetric synthesis, including both transition-metal-catalyzed and organocatalytic transformations.[3-5] Consequently, numerous strategies have been developed for the synthesis of 1,2-diamines, including diastereo- and enantioselective examples, with continued efforts to improve their efficiency and selectivity. One of the methods providing 1,2-diamines is the reaction of a nitrogen-nucleophile opening an aziridine ring. Interest in this small heterocycle is dictated either by biological activity, mainly as antitumor agents, displayed by some naturally occurring compounds bearing the aziridine ring or by the ring strain of those spring-loaded heterocycles that make them useful precursors of more complex molecules.[6-8] The highly strained three-membered ring readily opens with excellent stereo- and regioselectivity to afford a wide variety of more stable ring-opened or ring-expanded amines. Chiral aziridines have found widespread use in organic synthesis. They can act as sources of chirality in stereocontrolled reactions and have found use both as ligands and chiral auxiliaries in asymmetric synthesis.[9-12] On the other hand, it is very surprising that diamines containing one aziridine ring and other amine functions remain a little known group of compounds. The first synthesis of enantiopure 2-aminoalkylaziridines was performed by Concellón in 2001.[13] However, the aminoalkylaziridines obtained were limited to aziridine derivatives containing a tertiary *N,N*-dibenzylamine group exclusively. Recently, a new and original method of synthesis of aziridine-containing vicinal diamines from aziridine aldehyde dimers was described by Yudin. Interestingly, all of the synthesized optically pure aminoalkylaziridines were then subjected to ring-opening reactions,[14,15] but to the best of our knowledge they have not been tested as ligands or organocatalysts in asymmetric synthesis. At this point it should be mentioned that enantiomerically pure aziridine derivatives (alcohols, semicarbazides, sulfoxides, ethers) strongly coordinate to zinc species, exhibiting excellent catalytic properties in asymmetric reactions performed in the presence of zinc ions,[12] namely the addition of diethylzinc and phenylethynylzinc[16-20] to various carbonyl compounds or in $Zn(OTf)_2$-catalyzed aldol condensation.[21,22]

The synthetic diversity and broad mode of application of chiral diamines prompted us to explore the synthesis of optically pure aziridine-containing diamines. Our efforts were focused on developing a method of synthesis of optically pure diamines in which the chiral aziridine ring would bear a β-aminoalkyl group on the nitrogen atom. The anticipated products were obtained from optically pure aziridines.

Results and Discussion

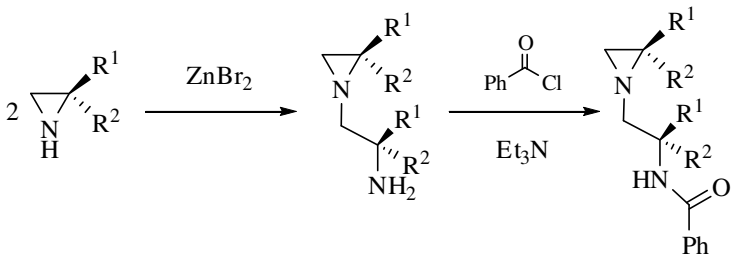
Aziridines can be divided into two categories depending on the nature of the *N*-substituent. Activated aziridines contain a strongly electronegative substituent, such as an *N*-tosyl or *N*-acyl group that facilitates their ring-opening reactions. Non-activated aziridines, such as *N*-alkyl or unsubstituted aziridines, do not undergo this reaction or react much less easily. For these, both protic (HCl, H_2SO_4, TfOH) and Lewis acids (BF_3·OEt, $Yb(OTf)_3$, $Cu(OTf)_2$) were reported to induce the aziridine ring-opening reaction.

The aziridine ring-opening reaction with aziridine itself[23] has been known for a long time in coordination chemistry and was named 'dimerization' of aziridines. However, this reaction has been described in only a few papers and concerns specific reactions, namely, the synthesis of complexes of aziridines with transition metals. Transition metal (Cr, Mo, W, Cd, Co)-mediated ring-opening reactions of aziridine ligands yielding aminoethylaziridine-*N,N*' complexes by 'aziridine dimerization' were first observed by Beck[24] and Fritz[25] and then by others.[26,27] Recently, synthesis, X-ray structural characterization, antimicrobial and cytotoxic effects of aziridine and 1-(2-aminoethyl)aziridine complexes of Cu(II) and Pd(II) have been reported.[28] Moreover, this transformation can take place spontaneously without Lewis acid in a strongly limited way, when aziridine is stored at room temperature.[29] It should be stressed that in the above examples, all of the reactions were focused on the synthesis of appropriate complexes, not on the synthesis of the aminoalkyl-aziridines themselves, and the reactions were performed mainly with achiral aziridines. The primary purpose of our study was the synthesis of optically pure aminoalkylaziridines either based on the above 'aziridine dimerization' of optically pure aziridine or by cross-coupling of two different chiral aziridine molecules. The first case provides aminoalkylaziridines with the same hydrocarbon cores in the ring and in the chain, while the second case produces aminoalkylaziridines with different hydrocarbon cores and enables combinations thereof.

On the other hand, as we demonstrated previously, aziridine derivatives strongly coordinate to zinc halides to form a complex built from two molecules of aziridine and one molecule of zinc halide.[30-32] Such complexes were used for nucleophilic ring-opening of the aziridine ring with non-complexed aziridine itself. Taking into account the stoichiometry of the complex formed, by using one equivalent of $ZnBr_2$ and four equivalents of aziridine we can obtain a mixture consisting in one equivalent of the complex of $aziridine_2ZnBr_2$ and two equivalents of non-complexed aziridine. Therefore, this stoichiometric mixture of activated aziridine has the potential for the ring-opening reaction with non-activated aziridines which can play the role of a nucleophile.

In order to obtain 1,2-aminoalkylaziridine **2**, optically pure (*S*)-2-isopropylaziridine (**(*S*)-1a**) was used (Scheme 1). After optimization of the process (Table 1), the best results were in fact obtained in the reaction of four equivalents of aziridine **(*S*)-1a** with one equivalent of $ZnBr_2$ at 80 °C without any additional solvent. The expected product was isolated from the reaction mixture through the addition of a 20% aqueous solution of NaOH in order to decompose the complex of aziridine-Zn and *via* extraction of the aqueous solution with diethyl ether. The ethereal solution of the product was dried and the solvent and excess of the starting aziridine were removed under reduced pressure. A crude, but practically pure product was obtained in 50% yield. The reactions with (*R*)-2-isopropylaziridine (**(*R*)-1a**), (*S*)-2-isobutylaziridine (**1b**), (*S*)-2-benzylaziridine (**1c**) and achiral 2,2-dimethylaziridine (**1d**) under the same conditions were completed in similar yields (53%, 56%, 63%, 47%, respectively) after two hours. It is worth pointing out that the reaction is fully regio- and stereoselective. The nucleophilic attack takes place on the less substituted carbon atom and occurs with retention of configuration of the substrates. No other regio- or diastereoisomer was detected.

In the last step, aminoaziridines of type **2** were transformed into benzoylated derivatives **3** in order to confirm their structures. The chemical yields of the process were approximately 50%, however, the simplicity of our method makes it a synthetically useful tool.



(*S*)-**1a** R^1 = H, R^2=*i*-Pr
(*R*)-**1a** R^1 = *i*-Pr, R^2=H
1b R^1 = H, R^2=*i*-Bu
1c R^1 = H, R^2=Bn
1d R^1 = R^2=Me

(*S,S*)-**2a** R^1 = H, R^2=*i*-Pr
(*R,R*)-**2a** R^1 = *i*-Pr, R^2=H
2b R^1 = H, R^2=*i*-Bu
2c R^1 = H, R^2=Bn
2d R^1 = R^2=Me

(*S,S*)-**3a** R^1 = *i*-Pr, R^2=H
3b R^1 = H, R^2=*i*-Bu
3c R^1 = H, R^2=Bn
3d R^1 = R^2=Me

Scheme 1. Self-opening reactions of aziridines **1**.

Table 1. Optimization of the aziridine ring self-opening reaction

Entry	Aziridine **(*S*)-1a** (eq.)	Lewis acid $ZnBr_2$ (eq.)	Yield (%)
1	**8**	1	12
2	**4**	1	50
3	**2**	1	39
4	**4**	1 + 0.5[a]	49
5	**4**	1 ($BF_3{\cdot}Et_2O$)[b]	30[b]

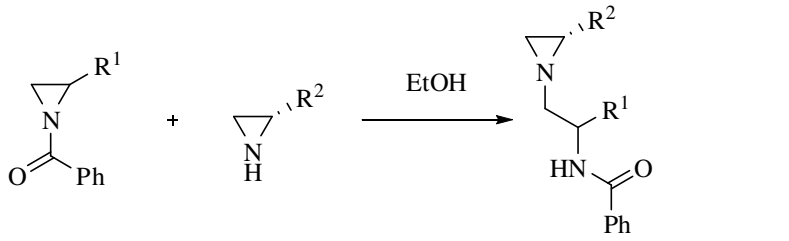
All reactions were performed in 2 h at 80 °C.
[a] Additional amount of $ZnBr_2$ was added after 1 h of heating.
[b] Reaction performed with $BF_3{\cdot}Et_2O$ instead of $ZnBr_2$, mixture after extraction contains impurities indicating the partial decomposition of aziridine.

It should be mentioned that when using this method, only 1,2-diamines containing the same hydrocarbon core in the ring and in the chain could be obtained. As an extension of our studies, ring-opening reactions using different aziridines were performed and this allowed us to synthesize vicinal aminoalkylaziridines with two different hydrocarbon cores. It is clear that in order to perform the ring-opening reaction, activation of the aziridine ring is required. A convenient method involves acylation of the nitrogen atom of aziridine. In our studies we used (*S*)-*N*-benzoyl-2-isopropylaziridine (**(*S*)-4a**), which was treated with aziridine **(*S*)-1a** in boiling ethanol. It should be noted that, as above, no other regio- or diastereoisomer was detected in the post-reaction mixture. The nucleophilic attack took place on the less substituted carbon atom.

Nucleophilic ring-opening reactions of activated aziridines afforded compound **(*S,S*)-3a** with slightly lower efficiency (Scheme 2). Aziridine **(*S,S*)-3a,** obtained by using two methods, was in a diastereomerically pure form, thus we claim that the self-opening reaction occurred with full stereoselectivity.

Based on the general protocol, the reactions of (*R*)-*N*-benzoyl-2-isopropylaziridine (**(*R*)-4a**) with (*S*)-2-methylaziridine **1e** (Scheme 2), and (*S*)-*N*-benzoyl-2-methylaziridine (**4b**) with aziridines **(*S*)-1a** and **(*R*)-1a**

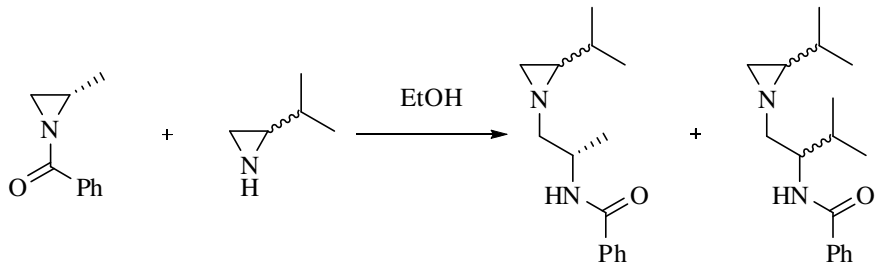
(Scheme 3), were performed. In all cases the expected products **3e-g** were isolated in approximately 30% yield.



(***S***)**-4a** R^1 = (*S*)-*i*-Pr (***S***)**-1a** R^2 = (*S*)-*i*-Pr (***S,S***)**-3a** R^1,R^2 = (*S*)-*i*-Pr
(***R***)**-4a** R^1 = (*R*)-*i*-Pr **1e** R^2 = (*S*)-Me **3e** R^1 = (*R*)-*i*-Pr, R^2 = (*S*)-Me

Scheme 2. Ring-opening reactions of aziridines leading to derivatives **3**.

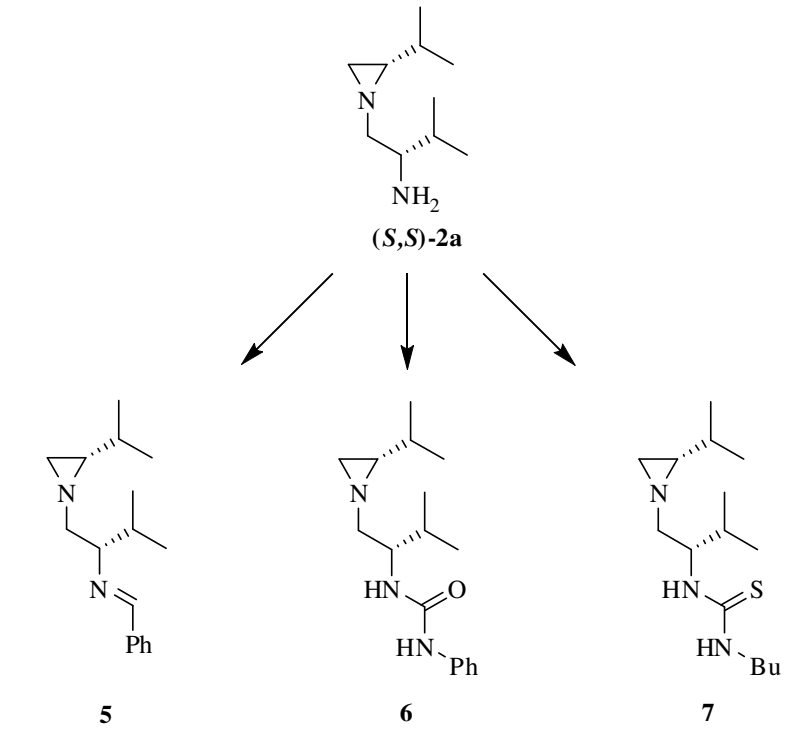
Unexpectedly, when we were using the 2-methylaziridine derivative **4b** we were able to isolate, besides the expected main products, compounds **(*S,S*)-3a**, **(*R,R*)-3a** as byproducts (ca. 10%, Scheme 3). Formation of these products is explained by a transamidation reaction (transfer of the benzoyl group between both aziridines) and subsequent ring opening with an excess of 2-isopropylaziridine along with simultaneous removal of (*S*)-2-methylaziridine by evaporation of the more volatile component.



4b (***S***)**-1a** (***R***)**-1a** **3f** (*S*)-*i*-Pr **3g** (*R*)-*i*-Pr (***S,S***)**-3a** (***R,R***)**-3a**

Scheme 3. Ring-opening reactions of aziridines leading to derivatives **3**.

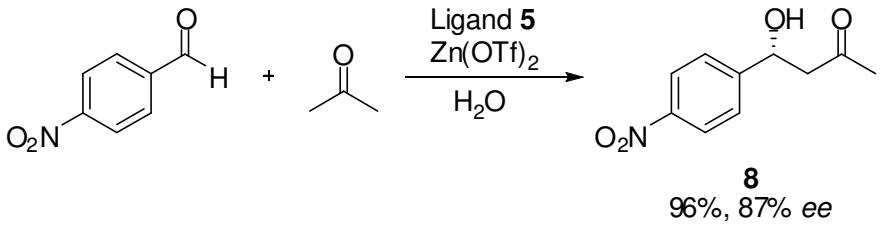
Based on our interest in the synthesis of new classes of ligands/catalysts for asymmetric synthesis, we decided to set up some experiments with different electrophiles leading to privileged groups of ligands. Three different reactions with an aldehyde, isocyanate and isothiocyanate were performed to obtain compounds containing the aziridine ring as a tertiary amine function and another amine-based subunit. These processes led us to produce ligands bearing imine, urea and thiourea motifs, respectively (Scheme 4).



Scheme 4. Reactions of aminoaziridine **(*S,S*)-2a** with various electrophiles.

The reaction of aminoaziridine **(*S,S*)-2a** with an equimolar amount of benzaldehyde in boiling methanol led to the desired product **5** in quantitative yield after 16 hours. Compound **(*S*)-2a** also easily reacted with phenyl isocyanate in THF at room temperature. Substitution product **6** was chromatographically isolated after eight hours reaction in 56% yield. In an analogous experiment we tried to obtain the corresponding thiourea derivative *via* reaction with phenyl isothiocyanate, but all attempts led to decomposition of the product. On the other hand, the reaction with butyl isothiocyanate was complete within 16 hours and compound **7** was obtained after chromatographic purification in 49% yield.

Finally we decided to check the catalytic activity of compound **5** in stereo-controlled asymmetric aldol condensation. The reactions were performed using 4-nitrobenzaldehyde in the presence of 5 mol% of catalyst and 5 mol% of zinc trifluoromethanesulfonate $Zn(OTf)_2$ in a mixture of acetone/water (1.8/0.2) (Scheme 5). After 72 h, reaction product **8** was isolated *via* column chromatography with 96% yield and 87% enantiomeric excess.



Scheme 5. Asymmetric aldol condensation in the presence of compound **5**.

Conclusion

A convenient synthesis of optically pure 1-(2-aminoalkyl)aziridines is described. Optically pure secondary aziridines can act as nucleophiles in the ring-opening reactions of activated aziridines or aziridine-$ZnBr_2$ complexes, leading to optically pure products. These chiral building blocks can be easily synthesized from readily available starting materials. The 1-(2-aminoalkyl)aziridines have the potential to be used as chiral diamine building blocks for organic synthesis as well as chiral polydentate ligands for asymmetric catalysis. We showed that imines prepared from a 1-(2-aminoalkyl)aziridine are efficient catalysts for asymmetric direct aldol condensation of aromatic aldehydes and acetone in the presence of water and zinc triflate. Further reactivity of these compounds is under investigation.

Experimental Section

General. The ^{1}H- (600 MHz), ^{13}C{^{1}H}- (150 MHz) spectra were measured on a Bruker Avance III instrument using solvent signals as reference. Chemical shifts (δ) are given in ppm and coupling constants *J* in Hz. Assignments of signals in ^{13}C-NMR spectra were made on the basis of HMQC experiments. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter with a sodium lamp at room temperature (*c* 1). Column chromatography was carried out using Merck 60 silica gel. TLC was performed on Merck 60 F_{254} silica gel plates. Visualization was accomplished with UV light (254 nm) or using iodine vapors. Solvents, reagents and starting materials were directly used as obtained commercially.

General procedure for cyclization of aziridine 1 in the presence of $ZnBr_2$. A solution of aziridine **1** (4 mmol) and $ZnBr_2$ (1 mmol) was stirred for 2 h at 80 °C. After this time the reaction mixture was treated with Et_2O and 20% NaOH, extracted twice, organic layer were dried end evaporated yielding product **2**.

(2*S*)-1-[(2*S*)-2-Isopropylaziridin-1-yl]-3-methyl-butan-2-amine ((*S,S*)-2a). Colorless oil, yield 50%, 0.17 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +28. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.76–2.72 (1H, m); 2.29 (1H, dd, $^3J_{HH}$ 8.4, $^4J_{HH}$ 11.4); 2.10 (1H, dd, $^3J_{HH}$ 4.2, $^4J_{HH}$ 11.4); 1.75–1.69 (1H, m); 1.53 (1H, d, $^3J_{HH}$ 3.0); 1.50 (2H, br.s, N$\underline{H}_2$); 1.31–1.25 (1H, m); 1.19–1.14 (2H, m); 1.05 (3H, d, $^3J_{HH}$ 6.6, C$\underline{H}_3$); 0.94–0.90 (9H, m, 3C$\underline{H}_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 66.3 (CH_2); 56.7, 46.7 (2CH); 32.6 (CH_2); 31.6, 31.4 (2CH); 20.5, 19.5, 19.4, 17.2 (4CH_3). Anal. calcd for $C_{10}H_{22}N_2$ (170.18): C, 70.53; H, 13.02; N, 16.45. Found: C, 70.55; H, 13.01; N, 16.44.

(2*R*)-1-[(2*R*)-2-Isopropylaziridin-1-yl]-3-methyl-butan-2-amine ((*R,R*)-2a). Colorless oil, yield 53%, 0.18 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) -28. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.76–2.72 (1H, m); 2.29 (1H, dd, $^3J_{HH}$ 8.4, $^4J_{HH}$ 11.4); 2.10 (1H, dd, $^3J_{HH}$ 4.2, $^4J_{HH}$ 11.4); 1.75–1.69 (1H, m); 1.53 (1H, d, $^3J_{HH}$ 3.0); 1.50 (2H, br.s, N$\underline{H}_2$); 1.31–1.25 (1H, m); 1.19–1.14 (2H, m); 1.05 (3H, d, $^3J_{HH}$ 6.6, C$\underline{H}_3$); 0.94–0.90 (9H, m, 3C$\underline{H}_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 66.3 (CH_2); 56.7, 46.7 (2CH); 32.6 (CH_2); 31.6, 31.4 (2CH); 20.5, 19.5, 19.4, 17.2 (4CH_3). Anal. calcd for $C_{10}H_{22}N_2$ (170.18): C, 70.53; H, 13.02; N, 16.45. Found: C, 70.59; H, 13.00; N, 16.41.

(2*S*)-1-[(2*S*)-2-Isobutylaziridin-1-yl]-4-methyl-pentan-2-amine (2b). Colorless oil, yield 56%, 0.222 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +20. ^{1}H NMR (600 MHz, $CDCl_3$): δ_H 2.95–2.91 (1H, m); 2.14 (1H, dd, $^3J_{HH}$ 8.4, $^4J_{HH}$ 12.0); 1.99 (1H, dd, $^3J_{HH}$ 4.8, $^4J_{HH}$ 12.0); 1.75–1.69 (1H, m); 1.41 (1H, d, $^3J_{HH}$ 3.0); 1.37–1.23 (3H, m); 1.15–1.06 (4H, m); 0.88–0.82 (12H, m, 4C$\underline{H}_3$). ^{13}C NMR (150 MHz, $CDCl_3$): δ_C 69.2 (CH_2); 49.3 (CH); 45.1, 42.3 (2CH_2); 38.6 (CH); 33.8 (CH_2); 27.2, 24.7 (2CH); 23.5, 23.0, 22.5, 22.0 (4CH_3). Anal. calcd for $C_{12}H_{26}N_2$ (198.21): C, 72.66; H, 13.21; N, 14.12. Found: C, 72.56; H, 13.30; N, 14.13.

(2*S*)-1-[(2*S*)-2-benzylaziridin-1-yl]-3-phenyl-propan-2-amine (2c). Colorless oil, yield 63%, 0.335 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +14. ^{1}H-NMR ($CDCl_3$): δ_H 7.24–7.04 (10H, m, 10 aromatic H); 3.07–3.02 (1H, m); 2.72–2.75 (3H, m); 2.37

(1H, dd, $^3J_{HH}$ 8.4, $^4J_{HH}$ 12.0); 2.24 (1H, dd, $^3J_{HH}$ 4.2, $^4J_{HH}$ 11.4); 2.09 (1H, dd, $^3J_{HH}$ 9.0, $^4J_{HH}$ 12.0); 1.63–1.60 (1H, m); 1.38 (1H, d, $^3J_{HH}$ 3.6); 1.22 (1H, d, $^3J_{HH}$ 6.0). ^{13}C-NMR ($CDCl_3$): δ_C 139.7, 139.2 ($2C_q$ aromatic); 129.3, 128.8, 128.5, 128.4, 126.4, 126.2 (CH aromatic); 67.6 (CH_2); 52.9 (CH); 42.3 (CH_2); 39.6, 33.4 ($2CH_2$); 24.8 (CH). Anal. calcd for $C_{18}H_{22}N_2$ (266.18): C, 81.16; H, 8.32; N, 10.52. Found: C, 81.18; H, 8.30; N, 10.52.

1-(2,2-Dimethylaziridin-1-yl)-2-methyl-propan-2-amine (2d). Colorless oil, yield 47%, 0.134 g. ^{1}H-NMR ($CDCl_3$): δ_H 2.49 (1H, d, $^3J_{HH}$ 12.0); 2.01 (1H, d, $^3J_{HH}$ 12.0); 1.77 (1H, s); 1.69 (2H, br.s, NH_2); 1.20 (3H, s, CH_3); 1.14 (3H, s, CH_3); 1.12 (3H, s, CH_3); 1.10 (3H, s, CH_3); 1.08 (1H, s). ^{13}C-NMR ($CDCl_3$): δ_C 65.8 (CH_2); 50.7 (C_q); 42.6 (CH_2); 34.9 (C_q); 28.8, 28.7, 26.7, 17.5 ($4CH_3$). Anal. calcd for $C_8H_{18}N_2$ (142.15): C, 67.55; H, 12.75; N, 19.69. Found: C, 67.56; H, 12.80; N, 19.63.

General procedure for synthesis of compounds 3. A solution of amine **2** (1 mmol), Et_3N (1.1 mmol) in Et_2O (5 ml), a mixture of benzoyl chloride (1 mmol) in Et_2O (1.5 ml) was added and stirred for 2 h at room temperature. After this time the reaction mixture was filtered, evaporated and product was purified by flash chromatography (SiO_2, hexane/AcOEt in gradient).

***N*-[(1*S*)-1-[[(2*S*)-2-Isopropylaziridin-1-yl]methyl]-2-methyl-propyl]benzamide ((*S,S*)-3a).** Colorless oil, yield 40%, 0.11 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +41. ^{1}H-NMR ($CDCl_3$): δ_H 7.11–7.69 (2H, m, 2 aromatic H); 7.43–7.35 (3H, m, 3 aromatic H); 6.27 (1H, br. s, NH); 3.99–3.94 (1H, m); 2.40 (1H, dd, $^3J_{HH}$ 6.0, $^4J_{HH}$ 12.0); 2.31 (1H, dd, $^3J_{HH}$ 4.8, $^4J_{HH}$ 12.0); 2.23–2.17 (1H, m); 1.50 (1H, d, $^3J_{HH}$ 3.0); 1.24–1.14 (3H, m); 0.95–0.91 (9H, m, $3CH_3$); 0.83 (3H, d, $^3J_{HH}$ 6.6, CH_3). ^{13}C-NMR ($CDCl_3$): δ_C 167.2 (C=O); 135.2 (C_q aromatic); 131.3, 128.6, 126.8 (CH aromatic); 61.7 (CH_2); 55.1, 46.4 (2CH); 33.0 (CH_2); 31.3, 29.4 (2CH); 20.4, 19.7, 19.4, 17.9 ($4CH_3$). Anal. calcd for $C_{17}H_{26}N_2O$ (274.20): C, 74.41; H, 9.55; N, 10.21; O, 5.83. Found: C, 74.40; H, 9.56; N, 10.23; O, 5.81.

***N*-[(1*S*)-1-[[(2*S*)-2-Isobutylaziridin-1-yl]methyl]-3-methyl-butyl]benzamide (3b).** Colorless oil, yield 34%, 0.103 g, $[\alpha]_D$ (c=0.2, $CHCl_3$) +39. ^{1}H-NMR ($CDCl_3$): δ_H 7.82–7.80 (2H, m, 2 aromatic H); 7.53–7.4 (3H, m, 3 aromatic H); 6.43 (1H, br. s, NH); 4.34–4.30 (1H, m); 2.64 (1H, dd, $^3J_{HH}$ 6.0, $^4J_{HH}$ 12.0); 2.29 (1H, dd, $^3J_{HH}$ 3.6, $^4J_{HH}$ 12.0); 1.80–1.71 (2H, m); 1.67–1.64 (1H, m); 1.55 (1H, d, $^3J_{HH}$ 3.6); 1.47–1.44 (1H, m); 1.32 (1H, d, $^3J_{HH}$ 6.6); 1.14–1.10 (1H, m); 1.01–0.96 (12H, m, $4CH_3$). ^{13}C-NMR ($CDCl_3$): δ_C 166.8 (C=O); 135.0 (C_q aromatic); 131.2, 128.5, 126.9 (CH aromatic); 64.4 (CH_2); 48.3 (CH); 42.4, 42.2 ($2CH_2$); 38.9 (CH); 34.1 (CH_2); 27.1, 25.1 (2CH); 23.2, 23.0, 22.5, 22.3 ($4CH_3$). Anal. calcd for $C_{19}H_{30}N_2O$ (302.24): C, 75.45; H, 10.00; N, 9.26; O, 5.29. Found: C, 75.40; H, 10.01; N, 9.28; O, 5.31.

***N*-[(1*S*)-1-Benzyl-2-[(2*S*)-2-benzylaziridin-1-yl]ethyl]benzamide (3c).** Colorless oil, yield 39%, 0.144 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +39. ^{1}H-NMR ($CDCl_3$): δ_H 7.64–7.62 (2H, m, 2 aromatic H); 7.43–7.33 (3H, m, 3 aromatic H); 7.23–7.08 (10H, m, 10 aromatic H); 6.48 (1H, br. s, NH); 4.28–4.22 (1H, m); 2.90 (1H, dd, $^3J_{HH}$ 6.6, $^4J_{HH}$ 13.8); 2.80 (1H, dd, $^3J_{HH}$ 7.8, $^4J_{HH}$ 13.8); 2.69–2.67 (2H, m); 2.48 (1H, dd, $^3J_{HH}$ 5.4, $^4J_{HH}$ 12.0); 2.21 (1H, dd, $^3J_{HH}$ 4.2, $^4J_{HH}$ 12.0); 1.68–1.67 (1H, m); 1.62 (1H, d, $^3J_{HH}$ 3.0); 1.26 (1H, d, $^3J_{HH}$ 6.0). ^{13}C-NMR ($CDCl_3$): δ_C 166.9 (C=O); 139.3, 138.2, 134.9 ($3C_q$ aromatic); 131.3, 129.3, 128.9, 128.6, 128.5, 128.4, 128.3, 126.9, 126.4 (CH aromatic); 61.7 (CH_2); 51.2 (CH); 41.0 (CH); 39.4, 38.2 ($2CH_2$); 33.7 (CH_2). Anal. calcd for $C_{25}H_{26}N_2O$ (370.21): C, 81.05; H, 7.07; N, 7.56; O, 4.32. Found: C, 81.11; H, 7.06; N, 7.55; O, 4.28.

***N*-[2-(2,2-Dimethylaziridin-1-yl)-1,1-dimethyl-ethyl]benzamide (3d).** Colorless oil, yield 21%, 0.052 g. ^{1}H-NMR ($CDCl_3$): δ_H 7.70–7.69 (2H, m, 2 aromatic H); 7.39–7.32 (3H, m, 3 aromatic H); 7.27 (1H, br. s, NH); 2.64 (1H, d, $^3J_{HH}$ 12.0); 2.16 (1H, d, $^3J_{HH}$ 12.0); 1.72 (1H, s); 1.43, 1.42 (6H, 2s, $2CH_3$); 1.16 (3H, s, CH_3); 1.12 (1H, s); 1.10 (3H, s, CH_3). ^{13}C-NMR ($CDCl_3$): δ_C 166.8 (C=O); 136.3 (C_q aromatic); 130.9, 128.4, 126.8 (CH aromatic); 63.0 (CH_2); 53.8 (C_q); 42.3 (CH_2); 35.3 (C_q); 27.6, 26.6, 25.2, 17.7 ($4CH_3$). Anal. calcd for $C_{15}H_{22}N_2O$ (246.17): C, 73.13; H, 9.00; N, 11.37; O, 6.49. Found: C, 73.14; H, 9.00; N, 11.36; O, 6.49.

General procedure for reaction of benzoylaziridine 4 with aziridine 1. A solution of compound **4** (1 mmol) and aziridine **1** (3 mmol) in absolute ethanol (15 ml) was stirred for 18 h at 80 °C. After this time the reaction mixture was evaporated and product was purified by flash chromatography (SiO_2, hexane/AcOEt in gradient).

***N*-[(1*S*)-2-Methyl-1-[[(2*S*)-2-methylaziridin-1-yl]methyl]propyl]benzamide (3e).** Colorless oil, yield 30%, 0.074 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +12. ^{1}H-NMR ($CDCl_3$): δ_H 7.82–7.81 (2H, m, 2 aromatic H); 7.52–7.44 (3H, m, 3 aromatic H); 6.48 (1H, br. s, NH); 4.11–4.06 (1H, m); 2.62 (1H, dd, $^3J_{HH}$ 6.0, $^4J_{HH}$ 12.6); 2.35 (1H, dd, $^3J_{HH}$ 4.8, $^4J_{HH}$ 12.6); 2.16–4.10 (1H, m); 1.55 (1H, d, $^3J_{HH}$ 3.6); 1.43–1.39 (1H, m); 1.36 (3H, d, $^3J_{HH}$ 6.6, CH_3); 1.15 (3H, d, $^3J_{HH}$ 5.4, CH_3); 1.02 (6H, ps. t, $^3J_{HH}$ 6.6, $2CH_3$). ^{13}C-NMR ($CDCl_3$): δ_C 167.0 (C=O); 135.0 (C_q aromatic); 131.2, 128.7, 126.6 (CH aromatic); 65.5 (CH_2); 46.7, 45.9 (2CH); 34.0 (CH_2); 31.3 (CH); 20.5, 19.5, 19.1 ($3CH_3$). Anal. calcd for $C_{15}H_{22}N_2O$ (246.17): C, 73.13; H, 9.00; N, 11.37; O, 6.49. Found: C, 73.10; H, 9.01; N, 11.37; O, 6.51.

***N*-[(1*S*)-2-[(2*S*)-2-Isopropylaziridin-1-yl]-1-methyl-ethyl]benzamide (3f).** Colorless oil, yield 31%, 0.076 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +33. ^{1}H-NMR ($CDCl_3$): δ_H 7.71–7.68 (2H, m, 2 aromatic H); 7.42–7.34 (3H, m, 3 aromatic H); 6.47 (1H, br. s, NH); 4.18–4.13 (1H, m); 2.44 (1H, dd, $^3J_{HH}$ 6.6, $^4J_{HH}$ 12.0); 2.21 (1H, dd, $^3J_{HH}$ 4.2, $^4J_{HH}$ 12.0); 1.51 (1H, d, $^3J_{HH}$ 3.6); 1.31 (3H, d, $^3J_{HH}$ 6.6, CH_3); 1.29–1.16 (3H, m); 0.96, 0.84 (6H, 2d, $^3J_{HH}$ 6.6, $2CH_3$). ^{13}C-NMR ($CDCl_3$): δ_C 166.8 (C=O); 134.9 (C_q aromatic); 131.3, 128.5, 126.9 (CH aromatic); 65.6 (CH_2); 46.8, 46.0 (2CH); 32.5 (CH_2); 31.2 (CH); 20.6, 19.3, 19.1 ($3CH_3$). Anal. calcd for $C_{15}H_{22}N_2O$ (246.17): C, 73.13; H, 9.00; N, 11.37; O, 6.49. Found: C, 73.23; H, 8.98; N, 11.33; O, 6.45.

***N*-[(1*S*)-2-[(2*R*)-2-Isopropylaziridin-1-yl]-1-methyl-ethyl]benzamide (3g).** Colorless oil, yield 29%, 0.071 g, $[\alpha]_D$ (c=0.2, $CHCl_3$) +9. ^{1}H-NMR ($CDCl_3$): δ_H 7.83–7.80 (2H, m, 2 aromatic H); 7.55–7.43 (3H, m, 3 aromatic H); 6.82 (1H, br. s, NH); 4.26–4.21 (1H, m); 2.48 (1H, dd, $^3J_{HH}$ 6.6, $^4J_{HH}$ 12.0); 2.39 (1H, dd, $^3J_{HH}$ 4.2, $^4J_{HH}$ 12.0); 1.66 (1H, d, $^3J_{HH}$ 3.6); 1.36 (3H, d, $^3J_{HH}$ 6.6, CH_3); 1.30–1.16 (3H, m); 0.99, 0.92 (6H, 2d, $^3J_{HH}$ 6.6, $2CH_3$). ^{13}C-NMR ($CDCl_3$): δ_C 167.0 (C=O); 135.1 (C_q aromatic); 131.2, 128.6, 126.9 (CH aromatic); 65.5 (CH_2); 46.3, 45.3 (2CH); 34.1 (CH_2); 31.3 (CH); 20.3, 19.5, 19.0 ($3CH_3$). Anal. calcd for $C_{15}H_{22}N_2O$ (246.17): C, 73.13; H, 9.00; N, 11.37; O, 6.49. Found: C, 73.01; H, 9.03; N, 11.40; O, 6.55.

Synthesis of (*E*)-*N*-[(1*S*)-1-[[(2*S*)-2-isopropylaziridin-1-yl]methyl]-2-methyl-propyl]-1-phenyl-methanimine (5). A solution of **(*S,S*)-2a** (1 mmol, 0.17 g) and benzaldehyde (1 mmol, 0.106 g) in MeOH (10 ml) were refluxed for 16 h. After this time the reaction mixture was evaporated and product was purified by flash chromatography (SiO_2, hexane/AcOEt in gradient) to obtain **5** as a colorless oil, yield 98%, 0.253 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +4. ^{1}H-NMR ($CDCl_3$): δ_H 8.31 (1H, s, CH); 7.78–7.76 (2H, m, 2 aromatic H); 7.44–7.42 (3H, m, 3 aromatic H); 3.24–3.22 (1H, m); 3.03 (1H, dd, $^3J_{HH}$ 4.8, $^4J_{HH}$ 12.0); 2.12 (1H, dd, $^3J_{HH}$ 7.2, $^4J_{HH}$ 12.0); 2.03–2.01 (1H, m); 1.55 (1H, d, $^3J_{HH}$ 3.0); 1.22–1.20 (3H, m); 0.99–0.93 (6H, m, $2CH_3$); 0.85, 0.79 (6H, 2d, $^3J_{HH}$ 6.6, $2CH_3$). ^{13}C-NMR ($CDCl_3$): δ_C 160.4 (CH=N); 136.7 (C_q aromatic); 130.3, 128.5, 128.2 (CH aromatic); 77.6 (CH); 64.8 (CH_2); 47.0, 31.6 (2CH); 31.4 (CH_2); 30.9 (CH); 20.6, 20.0, 18.9, 18.1 ($4CH_3$). Anal. calcd for $C_{17}H_{26}N_2$ (258.21): C, 79.02; H, 10.14; N, 10.84. Found: C, 79.03; H, 10.15; N, 10.82.

Synthesis of 1-[(1*S*)-1-[[(2*S*)-2-isopropylaziridin-1-yl]methyl]-2-methyl-propyl]-3-phenyl-urea (6). A solution of **(*S,S*)-2a** (1 mmol, 0.17 g) and phenyl isocyanate (1 mmol, 0.119 g) in anhydrous THF (10 ml) were stirred for 8 h. After this time the reaction mixture was evaporated and product was purified by flash chromatography (SiO_2, hexane/AcOEt in gradient) to obtain **6** as a colorless oil, yield 56%, 0.162 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +0.5. ^{1}H-NMR ($CDCl_3$): δ_H 7.24–7.18 (5H, m, 5 aromatic H); 6.95 (1H, br. s, NH); 4.78 (1H, br. s, NH); 3.57–3.52 (1H, m); 2.51–2.48 (1H, m); 2.09 (1H, dd, $^3J_{HH}$ 3.6, $^4J_{HH}$ 8.4); 1.97–1.92 (1H, m); 1.54 (1H, br. s); 1.19–1.15 (3H, m); 0.95, 0.89 (6H, 2d, $^3J_{HH}$ 6.0, $2CH_3$); 0.83 (6H, d, $^3J_{HH}$ 6.6, $2CH_3$). ^{13}C-NMR ($CDCl_3$): δ_C 156.6 (C=O); 139.4 (C_q aromatic); 129.1, 123.1, 120.4 (CH aromatic); 64.6 (CH_2); 56.6, 47.0 (2CH); 33.5 (CH_2); 31.6, 30.4 (2CH); 20.5, 19.5, 19.2, 17.8 ($4CH_3$). Anal. calcd for $C_{17}H_{27}N_3O$ (289.22): C, 70.55; H, 9.40; N, 14.52; O, 5.53. Found: C, 70.56; H, 9.41; N, 14.50; O, 5.53.

Synthesis of 1-butyl-3-[(1*S*)-1-[[(2*S*)-2-isopropylaziridin-1-yl]methyl]-2-methyl-propyl]thiourea (7). A solution of **(*S,S*)-2a** (1 mmol, 0.17 g) and butyl isothiocyanate (1 mmol, 0.115 g) in anhydrous THF (10 ml) were stirred for 16 h. After this time the reaction mixture was evaporated and product was purified by flash chromatography (SiO_2, hexane/AcOEt in gradient) to obtain **7** as a colorless oil, yield 49%, 0.14 g, $[\alpha]_D$ (*c*=0.2, $CHCl_3$) +6. ^{1}H-NMR ($CDCl_3$): δ_H 5.87 (1H, br. s, NH); 3.62–3.58 (1H, m); 3.47–3.44 (2H, m); 2.84 (1H, br. s, NH); 2.01–1.96 (2H, m); 1.65–1.54 (4H, m); 1.43–1.23 (5H, m); 1.02 (3H, d, $^3J_{HH}$ 6.6, CH_3); 0.98–0.93 (12H, m). ^{13}C-NMR ($CDCl_3$): δ_C 187.2 (C=S); 61.2 (CH_2); 56.2, 46.8 (2CH); 34.4, 33.7, 31.3 ($3CH_2$); 31.2, 29.8 (2CH); 20.6 (CH_2); 20.4, 20.2, 19.3, 18.3, 13.8 ($5CH_3$). Anal. calcd for $C_{15}H_{31}N_3S$ (285.22): C, 63.11; H, 10.94; N, 14.72; S, 11.23. Found: C, 63.02; H, 10.96; N, 14.75; S, 11.27.

General procedure for asymmetric aldol reaction. Acetone (1.8 ml) and H_2O (0.2 ml) were added to a vial containing the catalyst (0.025 mmol) and $Zn(OTf)_2$ (0.025 mmol). After vigorous stirring at rt for 15 min the *p*-nitrobenzaldehyde (1 mmol) was added, and the resulting mixture stirred at rt and monitored by TLC. After 72 h, the solvent was evaporated and the aldol product was purified by flash column chromatography (SiO_2, hexane/AcOEt in gradient). **(4*S*)-Hydroxy-4-(4-nitrophenyl)-butan-2-one** yield 96%, *ee* 87%. ^{1}H and ^{13}C spectra in agreement with literature.[33] The enantiomeric excess was determined by chiral HPLC (Chiral AD-H, ^{i}PrOH/*n*-hexane 10/90, flow: 1 ml/min., λ = 254 nm): t_R = 23.17 min. (minor), t_R = 24.06 min. (major).

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