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Solvent- and Temperature-Dependent Functionalisation of Enantioenriched Aziridines

Maria Carolina de Ceglie,[a] Biagia Musio,[a] Francesco Affortunato,[a] Anna Moliterni,[b] Angela Altomare,[b] Saverio Florio,[a] and Renzo Luisi*[a]

Abstract: A highly stereo- and regioselective functionalisation of chiral non-racemic aziridines is reported. By starting from a parent enantioenriched aziridine and finely tuning the reaction conditions, it is possible to address the regio- and stereoselectivity of the lithiation/electrophile trapping sequence, thereby allowing the preparation of highly enantioenriched functionalised aziridines. From chiral *N*-alkyl *trans*-2,3-diphenylaziridines (*S*,*S*)-**1a**,**b**, two differently configured chiral aziridinyllithiums could be generated (*trans*-**1a**,**b-Li** in toluene and *cis*-**1a**,**b-Li** in THF), thus disclosing a solvent-dependent reactivity that is useful for the synthesis of chiral tri-substituted aziridines with different stereochemistry. In contrast, chiral aziridine (*S*,*S*)-**1c** showed a temperature-dependent reactivity to give chiral *ortho*-lithiated aziridine **1c-*ortho*-Li** at −78 °C and α-lithiated aziridine **1c-α-Li** at 0 °C. Both lithiated intermediates react with electrophiles to give enantioenriched *ortho*- and α-functionalised aziridines. The reaction of all the lithiated aziridines with carbonyl compounds furnished useful chiral hydroxyalkylated derivatives, the stereochemistry of which was ascertained by X-ray and NMR spectroscopic analysis. The usefulness of chiral non-racemic functionalised aziridines has been demonstrated by reductive ring-opening reactions furnishing chiral amines that bear quaternary stereogenic centres and chiral 1,2-, 1,3- and 1,5-aminoalcohols. It is remarkable that the solvent-dependent reactivity observed with (*S*,*S*)-**1a**,**b** permits the preparation of both the enantiomers of amines (**11** and *ent*-**11**) and 1,2-aminoalcohols (**13** and *ent*-**13**) starting from the same parent aziridine. Interestingly, for the first time, a configurationally stable chiral α-lithiated aziridine (**1c-α-Li**) has been generated at 0 °C. In addition, *ortho*-hydroxyalkylated aziridines have been easily converted into chiral aminoalkyl phthalans, which are useful building blocks in medicinal chemistry.

Keywords: asymmetric synthesis · molecular dynamics · organolithiums · regioselectivity · stereoselectivity

Introduction

Organolithium-mediated stereoselective syntheses gained great importance in the modern synthetic chemistry of the last two decades and are nowadays also central to important industrial processes.[1] Nevertheless, research directed at the optimisation of reactions that involve organolithium reagents discloses that several experimental parameters may affect the outcome of such reactions.[2] In the case of hetero-substituted organolithium reagents such as oxiranyllithiums, the reaction conditions (i.e., solvent, temperature, presence of ligands) should be carefully chosen to avoid undesired side reactions and maximise the yields. In addition, the effective use of chiral hetero-substituted organolithiums requires information about their stereochemical integrity.[3] The above considerations continue to be true also for aziridines, which are now well established as useful and versatile building blocks in organic synthesis and medicinal chemistry.[4]

Among the available methodologies for the preparation of functionalised aziridines, the lithiation/trapping sequence of simple parent aziridines is growing in importance.[5] Several research efforts have shed light on the structural factors that allow for an easy and stereoselective decoration of azir-

[a] Dr. M. C. de Ceglie, Dr. B. Musio, Dr. F. Affortunato, Prof. S. Florio, Prof. Dr. R. Luisi
Dipartimento Farmaco Chimico
Università degli Studi di Bari "A. Moro"
Via E. Orabona, 4 70125 Bari (Italy)
Fax: (+39) 0805442539
E-mail: luisi@farmchim.uniba.it

[b] Dr. A. Moliterni, Dr. A. Altomare
Istituto di Cristallografia: IC-CNR sezione di Bari
Via Amendola, 122/O 70126 Bari (Italy)

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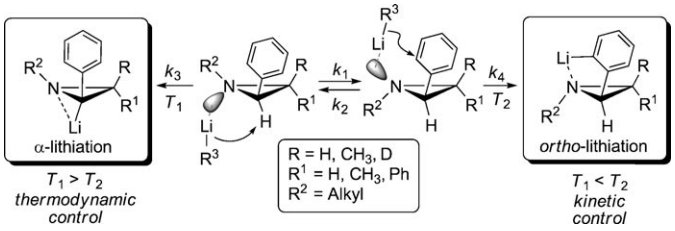
idines in their lithiated form, and recent mechanistic investigations have demonstrated that in *N*-alkyl arylaziridines the reaction conditions and aziridine nitrogen substitution can greatly affect the regio- and stereoselectivity of the lithiation reaction.[6]

For example, the α versus *ortho* competition observed in the lithiation of *N*-alkyl arylaziridines has been explained by a dynamically controlled reactivity that depends on the rate of the aziridine nitrogen inversion and complexation phenomena (Scheme 1). It has been found that starting from the same parent aziridine two different lithiated intermediates could be generated by finely tuning the reaction temperature.

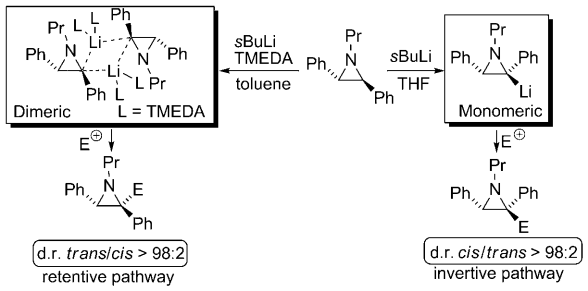


Scheme 1. Dynamically controlled reactivity.

Moreover, in addition to the nitrogen dynamics and complex induced proximity effect, it has been also demonstrated that the reaction solvent could affect the stereoselectivity of the lithiation/trapping sequence of *trans*-*N*-alkyl-2,3-diphenylaziridines.[7]

In particular, in a polar solvent such as THF, a complete inversion of configuration occurs upon quenching with an electrophile, whereas complete retention of the configuration is observed in a less polar solvent such as toluene. This opposite stereochemical outcome has been explained by a multinuclear magnetic resonance investigation and ascribed to two differently configured lithiated intermediates: a monomeric *cis*-configured lithiated aziridine in THF and a homochiral dimeric *trans*-configured lithiated aziridine in toluene (Scheme 2).[8]

In this latter case, a solvent-dependent reactivity occurred, and two stereochemical pathways (retentive or invertive) could be followed simply by starting from the same parent aziridine and just changing the reaction medium.



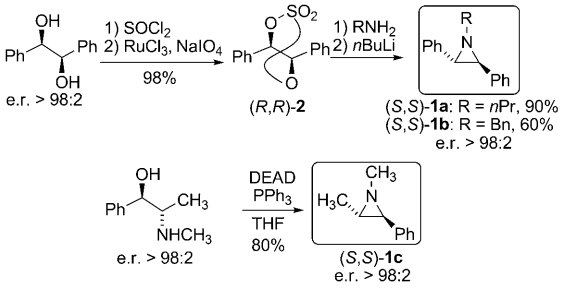
Scheme 2. Solvent-dependent reactivity (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylenediamine).

Interestingly, the above-described evidence suggests that a single starting material can serve for the preparation of completely different functionalised aziridines, thereby increasing the synthetic efficiency of such organolithium-mediated stereoselective transformations. Because we are aware of the importance of developing more efficient synthetic methodologies for the preparation of chiral molecules, and to assess both the efficiency and usefulness of temperature- and solvent-dependent reactivity, we wish to report here the results achieved in the lithiation/trapping of chiral enantioenriched aziridines.

Results and Discussion

For this study, two kinds of chiral non-racemic *N*-alkyl aziridines have been employed: an *N*-alkyl monophenylaziridine (to prove the temperature-dependent reactivity) and an *N*-alkyl 2,3-diphenylaziridine (to prove the solvent-dependent reactivity). Highly enantioenriched *trans*-*N*-alkyl-2,3-diphenylaziridines (*S*,*S*)-**1a**,**b** were easily obtained by starting from the commercially available chiral hydrobenzoin and using a reported protocol developed by Sharpless and coworkers.[9] Reaction of hydrobenzoin with $SOCl_2$ followed by oxidation furnished the cyclic sulfate (*R*,*R*)-**2**, which underwent a stereospecific ring-opening/ring-closing sequence in the presence of a primary amine and *n*BuLi (Scheme 3).

Chiral *N*-methyl-2-phenylaziridine (*S*,*S*)-**1c** could be prepared from commercially available (+)-ephedrine by cyclisation under Mitsunobu conditions (Scheme 3).[10]



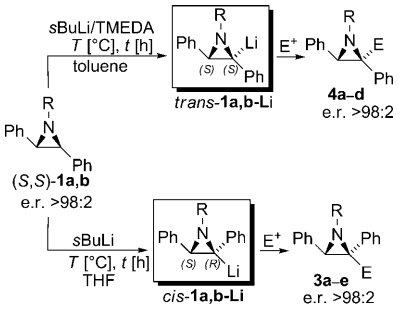
Scheme 3. Synthesis of enantioenriched *N*-alkyl arylaziridines (DEAD = diethyl azodicarboxylate).

With chiral aziridines (*S*,*S*)-**1a**–**c** in hand (e.r. > 98:2), the lithiation/electrophile trapping sequence was explored by finely tuning the reaction conditions (i.e., reaction solvent for (*S*,*S*)-**1a**,**b** and the temperature for (*S*,*S*)-**1c**).

The lithiation of both *trans*-aziridines (*S*,*S*)-**1a**,**b** with *s*BuLi in THF occurred with complete inversion of configuration to furnish, upon trapping with electrophiles, chiral trisubstituted aziridines **3a**–**e** (e.r. > 98:2). Conversely, the lithiation/electrophile trapping performed in toluene furnished highly enantioenriched (e.r. > 98:2) aziridines **4a**–**d** with complete retention of the configuration as a consequence of

a retentive pathway (Table 1). The two differently configured intermediates *trans*-**1a**,**b-Li** and *cis*-**1a**,**b-Li** are most likely involved in this highly stereoselective solvent-dependent transformation.[11]

Table 1. Solvent-dependent reactivity: lithiation/electrophile trapping sequence.



Product	R	T [°C]	t [h]	E	Yield [%][a]
3a	*n*Pr	−78	3	Et	92[b]
4a	*n*Pr	−78	4	Et	95[b]
3b	Bn	−78	1.5	Et	91[b]
4b	Bn	−84	1	Et	68[b]
3c	*n*Pr	−78	3	Me	98[c]
4c	*n*Pr	−78	4	Me	64[c]
3d	Bn	−78	1.5	*n*Pr	90[c]
4d	Bn	−84	1	*n*Pr	78[c]
3e	Bn	−78	1.5	$SiMe_3$	50[c,d]

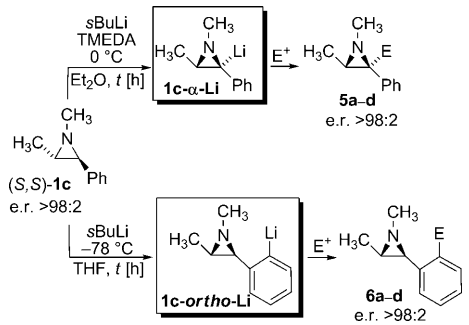
[a] Isolated yields. [b] Enantiomeric ratios ascertained by ^{1}H NMR spectroscopy (see the Supporting Information). [c] Enantiomeric ratios were assigned by analogy; no epimerisation was detected by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures. [d] Silylation in toluene occurs with inversion of configuration to furnish **3e** (see ref. [7]).

Next we turned our attention to aziridine (*S*,*S*)-**1c** to prove its temperature-dependent reactivity. When the lithiation was performed at 0 °C, the α-lithiated intermediate **1c-α-Li** was obtained and its trapping with electrophiles furnished highly enantioenriched (e.r. > 98:2) aziridines **5a–d** (Table 2).[12] It is remarkable that for the first time a configurationally stable enantioenriched aziridinyllithium has been generated at a relatively high temperature (0 °C), which is unusual for this kind of "fleeting" intermediates. It was also verified that **1c-α-Li** reacted with electrophiles with complete retention of the configuration with the exception of the silylation reaction.[13]

According to the model reported in Scheme 1, when performing the lithiation/trapping sequence at lower temperature (−78 °C), a complete switch of the regioselectivity was observed to obtain mainly *ortho*-lithiated intermediate **1c-*ortho*-Li**, which, upon reaction with electrophiles, gave chiral (e.r. > 98:2) aziridines **6a–d** (Table 2).

The regioselectivity switch (α/*ortho*) can be explained by taking into account the effect of the temperature on the rate of nitrogen inversion and complex induced proximity effect. At higher temperature (0 °C), the nitrogen inversion most likely occurs faster with respect to the rate of the deprotonation reaction, and the thermodynamically favoured benzylic position is lithiated. Conversely, at lower temperature

Table 2. Temperature-dependent reactivity: lithiation/electrophile-trapping sequence.



Product[a,b]	T [°C]	t [h]	E	Yield [%][c]
5a	0	3.5	Me	85
5b	0	3.5	Et	60
cis-**5c**[d]	0	3.5	$SiMe_3$	65
5d	0	3.5	$SnBu_3$	37
6a	−78	4	Me	85
6b	−78	4	Br	65
6c	−78	4	$SiMe_3$	88
6d	−78	4	$SnBu_3$	75

[a] Enantiomeric ratios evaluated by ^{1}H NMR spectroscopy in the presence of Mosher's acid or by chiral HPLC (see the Supporting Information). [b] Any epimerisation was observed by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. [c] Isolated yields. [d] An inversion of configuration occurred with this electrophile. Such an inversion was verified by NOESY experiments.

(−78 °C), the nitrogen inversion is slower with respect to the deprotonation reaction and the kinetic position becomes preferred.[14] In both cases, highly enantioenriched lithiated intermediates could be generated.

By reasoning that the trapping with carbonyl compounds would have provided hydroxyalkylated aziridines, which are useful in synthesis and catalysis,[15] this kind of lithiation/trapping sequence was then investigated on aziridines (*S*,*S*)-**1a–c**.

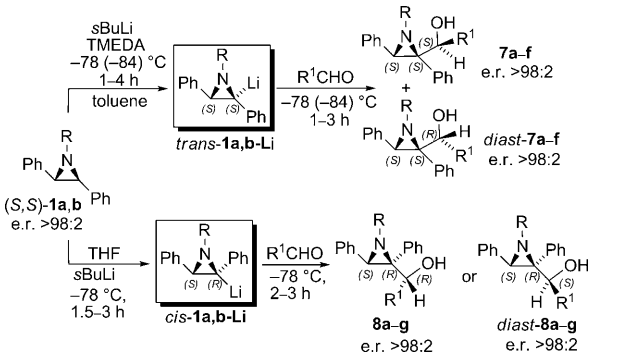
The solvent-dependent reactivity was first evaluated with aziridines (*S*,*S*)-**1a**,**b** to obtain the results reported in Table 3.

By running the lithiation/trapping sequence in toluene, the reactions with aldehydes occurred with complete retention of the configuration at the lithiated carbon but low stereoselectivity with reference to the newly created carbinolic carbon. Moreover, the almost equimolar mixtures of diastereomeric hydroxyalkylated aziridines **7a–f** and *diast*-**7a–f** could be easily separated by flash chromatography. The pure separated diastereomers were found to be highly enantioenriched (e.r. > 98:2).

As expected, when using THF as the reaction solvent, the lithiation/trapping with aldehydes occurred with complete inversion of the configuration at the lithiated carbon and, almost surprisingly, with a good to high level of stereocontrol at the newly created stereogenic centre, thereby furnishing highly enantioenriched hydroxyalkyl aziridines **8** and *diast*-**8**.

The reason for this different stereoselectivity upon switching from toluene to THF has been tentatively ascribed to

Table 3. Solvent-dependent reactivity: hydroxyalkylation reactions.



Product[a]	R	R^1CHO	Yield [%][b]	d.r.
7a/*diast*-**7a**	*n*Pr	PhCHO	77	49:51[c,d]
7b/*diast*-**7b**	*n*Pr	2-furylCHO	59	48:52[c]
7c/*diast*-**7c**	*n*Pr	2,4,6-$(CH_3)_3C_6H_2CHO$	49	48:52[c]
7d/*diast*-**7d**	*n*Pr	*t*BuCHO	65	44:56[c,d]
7e/*diast*-**7e**	Bn	PhCHO	48	47:53[c]
7f/*diast*-**7f**	Bn	2,4,6-$(CH_3)_3C_6H_2CHO$	45	57:43[c]
8a	*n*Pr	PhCHO	68	90:10[d,e]
8b	*n*Pr	2-furylCHO	77	88:12[f]
8c	*n*Pr	*t*BuCHO	62	98:2[e]
8d	Bn	PhCHO	56	87:13[d,e]
diast-**8e**	*n*Pr	2,4,6-$(CH_3)_3C_6H_2CHO$	54	2:98[d,e]
diast-**8f**	Bn	2,4,6-$(CH_3)_3C_6H_2CHO$	49	2:98[d,e]
8g/*diast*-**8g**	*n*Pr	2-CH_3-C_6H_4CHO	69	40:60[e]

[a] Enantiomeric ratios (>98:2) ascertained by ^{1}H NMR spectroscopic analysis (see the Supporting Information). [b] Overall isolated yields. [c] (*S*,*S*,*S*)/(*S*,*S*,*R*) diastereomeric ratio (see text). [d] Absolute and relative stereochemistry ascertained by X-ray analysis (see the Supporting Information). [e] (*S*,*R*,*R*)/(*S*,*R*,*S*) diastereomeric ratio (see text). [f] (*S*,*R*,*S*)/(*S*,*R*,*R*) diastereomeric ratio because of the higher priority of the 2-furyl group.

the different aggregation state of the lithiated aziridines (i.e., monomeric in THF and dimeric in toluene).[16] It is likely that complexation and aggregation phenomena could be responsible for the low stereoselectivity observed in toluene.

The relative and absolute stereochemistry of hydroxyalkylated aziridines of the kind **7**, *diast*-**7** and **8** were ascertained on the basis of ^{1}H NMR spectra, chromatographic evidence and by single-crystal X-ray analysis of some derivatives.

For derivatives **7a** and **7d**, both with a lower chromatographic R_f,[17] the crystallographic analysis furnished an (*S*,*S*,*S*) absolute configuration. In addition, it was found that all the diastereomers **7a–f** with a lower chromatographic R_f, showed a more shielded carbinolic methinic proton and a less shielded aziridine methinic proton with respect to the diastereomers with major R_f (see the Supporting Information). On the basis of this evidence, the (*S*,*S*,*S*) configuration was similarly assigned also to **7b**,**c** and **7e**,**f**. Consequently, compounds *diast*-**7a–f** should have an (*S*,*S*,*R*) configuration.[18,19]

The stereochemical analysis of hydroxyalkyl aziridines **8**, obtained in THF, was a little more complicated. The X-ray analyses of **8a**, **8d**, *diast*-**8e** and *diast*-**8f** assigned the (*S*,*R*,*R*) and (*S*,*R*,*S*) absolute configurations to **8a**,**d** and *diast*-**8e**,**f**, respectively.[20] A careful inspection of the ^{1}H NMR spectra revealed for the almost single isomer of *diast*-**8e** (d.r. 98:2) broad signals, which could likely be ascribed to a hindered rotation of the aryl groups induced by the two *ortho*-methyl substituents of the mesityl ring. In contrast, a 90:10 diastereomeric mixture of **8a** showed clear and sharp signals for the major isomer and featureless lumps for the minor isomer, thus suggesting the change of stereochemistry at the carbinolic carbon as responsible for this phenomenon. The presence of broad signals was also verified by ^{1}H NMR spectroscopic analysis of the crude reaction mixtures for the minor isomer of derivatives **8b** (d.r. 88:12) and **8d** (d.r. 87:13).[21] However, to prove the influence of the *ortho* substitution of the aldehyde on the stereoselectivity of the reaction, *o*-tolualdehyde was used for the trapping of *cis*-**1a-Li** in THF. Surprisingly, a modest degree of stereoselectivity was observed and two diastereomers, **8g** and *diast*-**8g** (d.r. 40:60), were isolated. This result seems to prove that the *ortho* substitution on the aromatic ring of the aldehyde could induce a switch on the stereoselectivity of the addition reaction.

Being unable to obtain suitable crystals, we decided to assign the stereochemistry of **8g** and *diast*-**8g** by comparison of their ^{1}H NMR spectra with that of compounds **8a** and *diast*-**8e** with known stereochemistry. Such a comparative ^{1}H NMR spectroscopic analysis was performed in [D_8]toluene at two different temperatures (298 and 348 K) on derivatives **8a** (as a 90:10 mixture of two diastereomers), *diast*-**8e**, **8g** and *diast*-**8g** (Figure 1). As depicted in Figure 1, more sharp signals were seen at 298 K for **8a** and **8g** (Figure 1a and b), whereas the minor isomer of **8a** (*diast*-**8a**) gave broad signals under the same conditions. In contrast, the ^{1}H NMR spectra of *diast*-**8e** and *diast*-**8g** showed broad signals at 298 K, which could likely be ascribed to a hampered rotation of the aryl groups due to their "similar" stereochemistry (Figure 1c and d).[22] When recording the ^{1}H NMR spectra at 348 K to overcome the rotational barrier, sharp signals were observed for all four hydroxyalkylated derivatives. Upon closer inspection, such spectra showed a similarity in chemical shifts for the pair **8a** and **8g** as well as for the pair *diast*-**8e** and *diast*-**8g**. In fact, the aziridinyl protons H_a ($\approx\delta=3.10$ ppm) in both **8a** and **8g** are more shielded with respect to $H_{a'}$ ($\approx\delta=3.5$ ppm) of *diast*-**8e** and *diast*-**8g**; in addition, methylenic protons H_b/H_c in both **8a** and **8g** showed similar chemical shifts, and a large $\Delta\delta$ ($\approx\delta=0.7$ ppm) as well as similar chemical shifts were found for $H_{b'}/H_{c'}$ of *diast*-**8e** and *diast*-**8g** that were associated with a smaller $\Delta\delta$ ($\approx\delta=0.35$ ppm). All this evidence prompted us to assign the (*S*,*R*,*R*) configuration to **8g** and the (*S*,*R*,*S*) configuration to *diast*-**8g**.

Once the stereochemistry of the hydroxyalkylated aziridines obtained in THF was established, a model that accounted for the stereoselectivity was needed. The observed stereochemistry has been tentatively rationalised by considering the monomeric tri-solvated structure of *cis*-**1a-Li**, demonstrated by NMR spectroscopy,[8] and the empirical model proposed by Bassindale and Taylor et al. for the reaction of chiral anions with carbonyl compounds.[23] In this

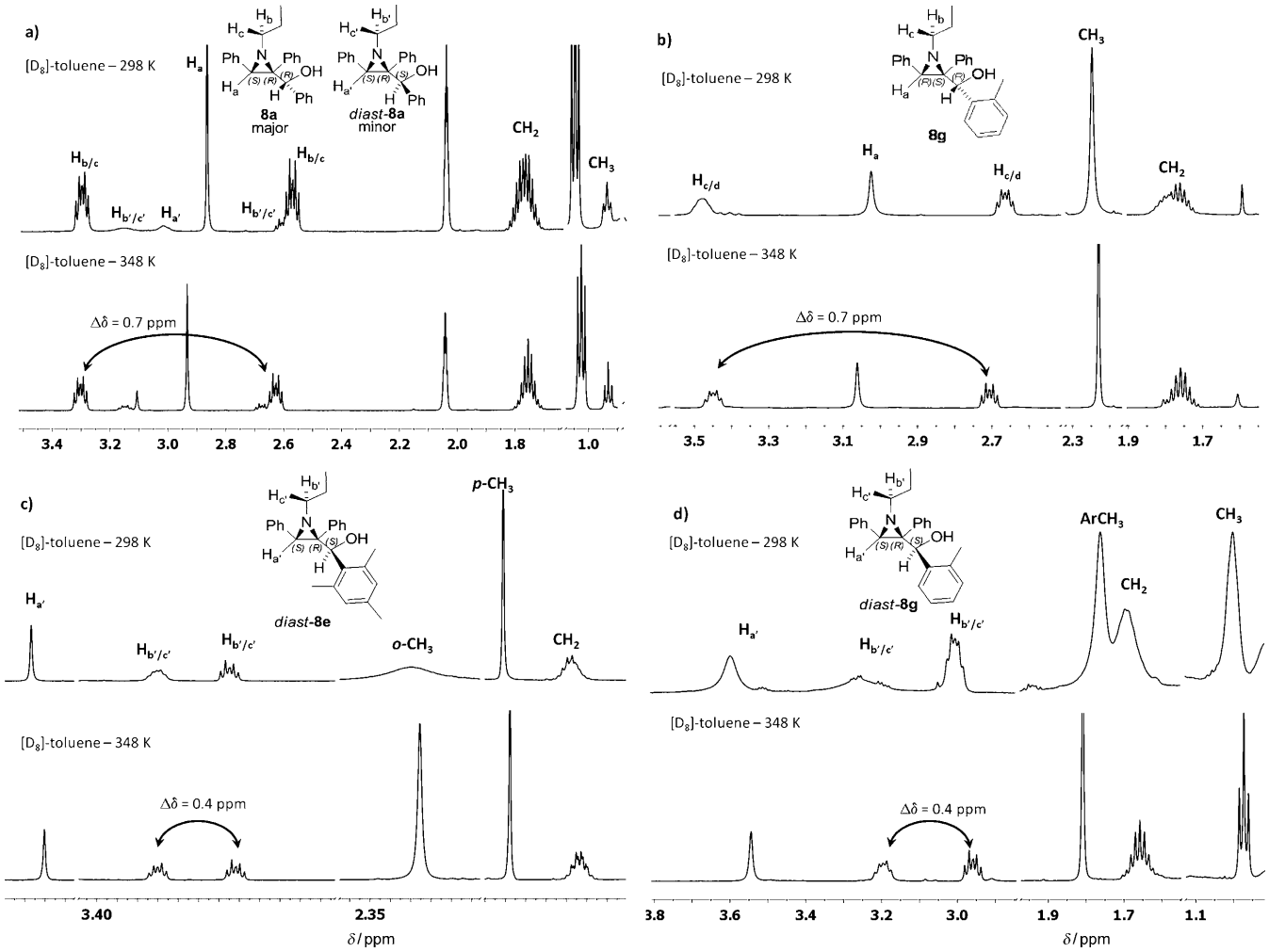
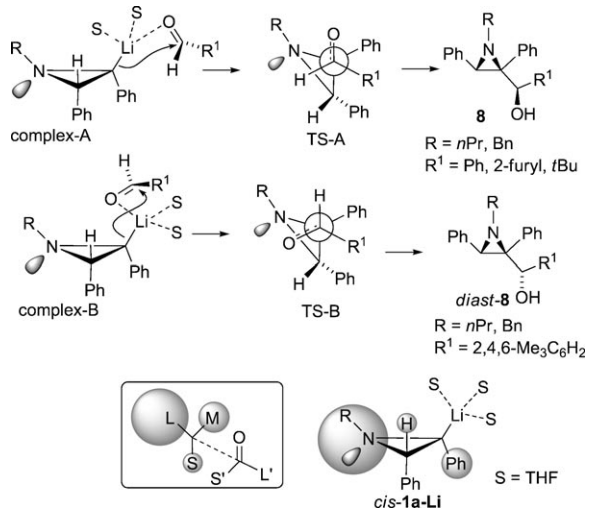


Figure 1. ^{1}H NMR spectroscopic analysis of hydroxyalkylated aziridines **8**.

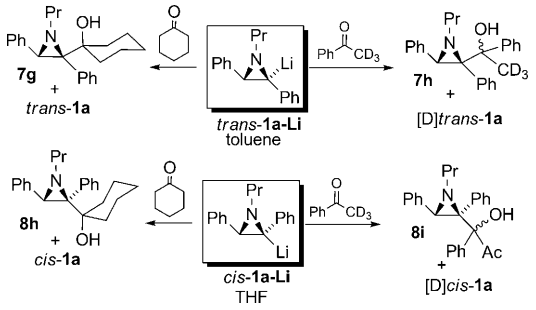
model, the large-, medium- and small-sized groups were assigned as depicted in Scheme 4. The nitrogen substituent was chosen as the large group, the lone pair being *trans*-configured with respect to the C–Li bond and the phenyl ring directly bonded to the lithiated carbon as medium group pointing away from the N substituent. The remaining proton was chosen as the small group.[24] It is reasonable to assume that the aldehyde approaches the anionic carbon by pointing its large substituent (L′) between the medium- and small-sized groups M and S. With the hypothesis that a complex between the carbonyl oxygen and the lithium (complexes A or B) could direct the approach of the aldehyde, two possible transition states could be proposed: TS-A in the reaction with unhindered aldehydes (i.e., benzaldehyde, 2-furfural and pivalaldehyde) that leads to derivatives **8**, and TS-B in the reaction with hindered aldehydes (i.e., mesityl aldehyde) that leads to derivatives *diast*-**8**. It is likely that with *o*-tolyl aldehyde both pathways could be followed, thereby leading to a modest stereoselectivity.[25]

The reactions of lithiated aziridines *cis*-**1a-Li** and *trans*-**1a-Li** with ketones were also explored but, unfortunately,



Scheme 4. Proposed model for the stereoselective synthesis of hydroxyalkylated aziridines **8**.

they were found to be more problematic. They occurred with very low yields and recovery of unreacted aziridines. In the reaction with cyclohexanone, for example, hydroxyalkylated products **7g**,**h** and **8h**,**i** were always obtained with variable amounts of protonated aziridines (*cis*-**1a** in THF and *trans*-**1a** in toluene) as the result of an acid–base reaction (Scheme 5). This hypothesis was confirmed by treating *cis*-



Scheme 5. Solvent-dependent reactivity: reaction with ketones.

1a-Li and *trans*-**1a-Li** with deuterium-labelled acetophenone. The main reaction products were deuterated aziridines [D]*cis*-**1a** and [D]*trans*-**1a** (in THF and toluene, respectively) together with traces of the corresponding hydroxyalkylated products. This different reactivity observed with ketones is still unclear and it is currently under investigation.

The hydroxyalkylation reaction was also investigated with aziridine (*S*,*S*)-**1c** to further prove its temperature-dependent reactivity. As expected, on the basis of the results reported in Table 2, the lithiation/trapping sequence performed at 0 °C gave α-functionalisation again to furnish enantioenriched derivatives **9a**–**c**. In contrast, when working at −78 °C, exclusive *ortho*-hydroxyalkylation was observed to achieve enantioenriched derivatives **10a**–**c** (Table 4).

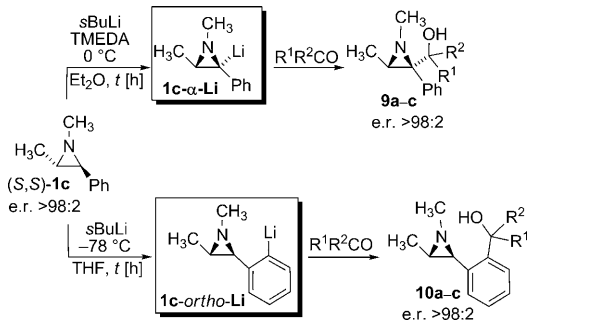
In this case, the reaction of **1c-α-Li** occurred with complete retention of the configuration at the lithiated carbon atom, and was successful also with enolisable ketones. The reaction with aldehydes occurred with poor stereoselectivity, with reference to the newly created stereogenic centre, for both **1c-α-Li** and **1c-*ortho*-Li**.

According to the above results, we were able to conclude that by using the same chiral scaffold and by just tuning finely the reaction parameters (i.e., solvent or temperature), it would be possible to prepare different chiral molecules by a simple lithiation/trapping sequence.

In fact, with functionalised aziridines in hand, we reasoned that they could be suitable starting materials for the preparation of chiral amines or aminoalcohols by using a simple reductive ring-opening reaction.[26]

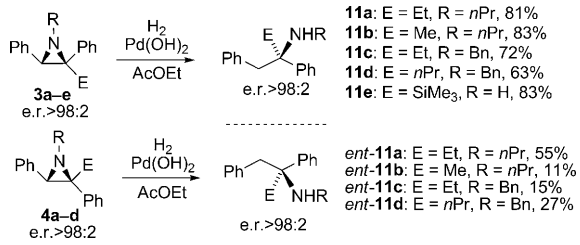
We were pleased to find that diastereomeric 2,3-diphenylaziridines **3a**–**e** and **4a**–**d** underwent a regioselective ring opening at the less-substituted benzylic carbon to furnish chiral amines **11a**–**e** and *ent*-**11a**–**d**, which bore quaternary stereogenic centres (Scheme 6).[27] Even if lower yields were observed in the reductive ring opening of some *trans*-aziri-

Table 4. Temperature-dependent reactivity: hydroxyalkylation reactions.



Product[a]	R^1R^2CO	*t* [h]	Yield [%][b]	d.r.[c]
9a	$(CH_2)_5CO$	3.5	82	–
9b	$(CH_2)_3CO$	3.5	84	–
9c/*diast*-**9c**[f]	*p*-ClC_6H_4CHO	3.5	70	50:50[d]
10a[e]	$(CH_2)_5CO$	4	54	–
10b	Ph_2CO	4	50	–
10c/*diast*-**10c**[g]	*p*-ClC_6H_4CHO	4	51	50:50[d]

[a] Enantiomeric ratios evaluated by ^{1}H NMR spectroscopy in the presence of Mosher's acid or by chiral HPLC (see the Supporting Information). [b] Isolated yields. [c] Evaluated by ^{1}H NMR spectroscopy on the crude reaction mixture. [d] Configuration at the newly created stereogenic centre assigned by X-ray analysis (see the Supporting Information). [e] Product **10a** underwent, upon flash chromatography, an intramolecular cyclisation reaction to furnish phthalan **17b** (see text). [f] The (*S*,*S*,*R*) configuration was assigned to **9c** based on crystallographic X-ray analysis (see the Supporting Information). [g] The (*S*,*S*,*S*) configuration was assigned to **10c** by crystallographic X-ray analysis (see the Supporting Information).

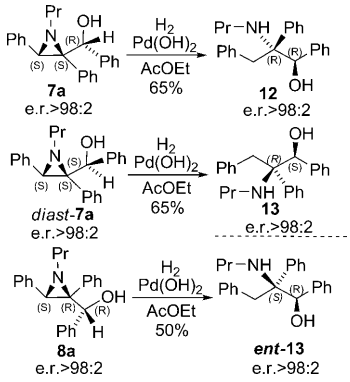


Scheme 6. Reductive ring opening of aziridines: synthesis of chiral amines.

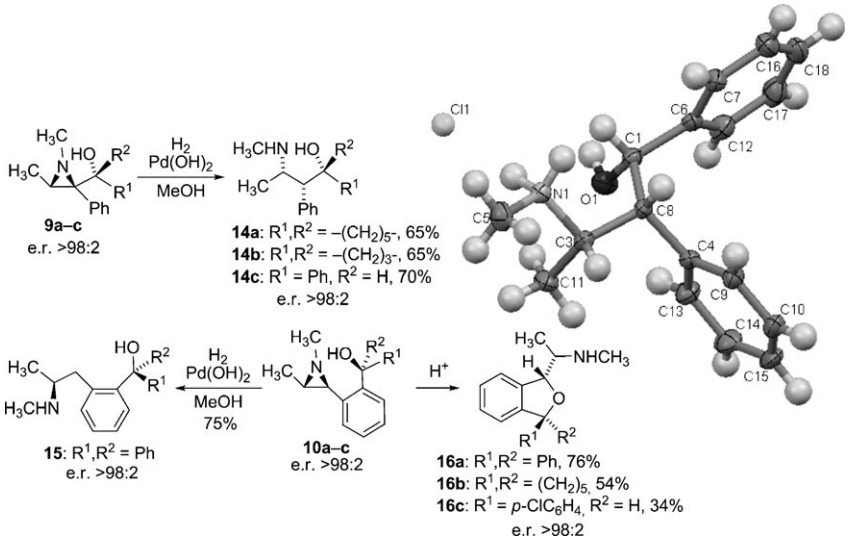
dines **4**,[28] it is noteworthy that both enantiomers of chiral amines could be obtained by using this methodology and both derived from the same chiral parent aziridine.[29]

The chance to apply the same synthetic protocol to the preparation of chiral aminoalcohols was also verified. Reduction of hydroxyalkylated aziridines **7a**, *diast*-**7a** and **8a** gave, respectively, aminoalcohols **12**, **13** and *ent*-**13** without loss of their optical purity (Scheme 7).[30] The enantiomeric relationship found between **13** and *ent*-**13** was also evidence of the correct stereochemistry assigned to *diast*-**7a**.[31]

For sake of comparison, the usefulness of hydroxyalkylated aziridines obtained in the temperature-dependent reactivity studies was also proven. Reductive ring opening of α-hydroxyalkylated aziridines **9a**–**c** provided chiral 1,3-aminoalcohol **14a**–**c** with good yields and high regioselectivity (Scheme 8). The stereochemistry of **14c** was assigned by



Scheme 7. Reductive ring opening of aziridines: synthesis of chiral 1,2-aminoalcohols.



Scheme 8. Synthesis of chiral 1,5-aminoalcohols and phthalans and crystal structure of **14c**·HCl.

single-crystal X-ray analysis on its chloridrate, and the same configuration was assigned by analogy to **14a**,**b** (see the Supporting Information).

Finally, it was realised that *ortho*-hydroxyalkylated aziridines could serve as starting materials for the preparation of two kinds of derivatives depending on the reaction conditions. Upon reduction, *ortho*-functionalised derivative **10b** furnished chiral non-racemic 1,5-aminoalcohol **15**. In addition, derivatives **10a–c** can serve also as useful starting materials for the preparation of enantioenriched phthalans **16a–c** by an acid-promoted intramolecular cyclisation reaction.[32]

It is worth pointing out again that by starting from the same chiral aziridine (*S*,*S*)-**1c**, useful chiral molecules with different structures can be obtained.

Conclusion

This work reports a highly stereo- and regioselective functionalisation of chiral aziridines.

With chiral *N*-alkyl *trans*-2,3-diphenylaziridines (*S*,*S*)-**1a**,**b**, it has been demonstrated that the solvent is able to induce a complete inversion of the stereochemical course of the reaction between the α-lithiated intermediates and the electrophiles. An invertive pathway is followed in THF in which monomeric *cis*-configured aziridinyllithiums *cis*-**1a**,**b-Li** are present, whereas a retentive pathway is observed in toluene, which can likely be ascribed to dimeric *trans*-configured aziridinyllithiums *trans*-**1a**,**b-Li**. This solvent-dependent reactivity has been nicely exploited for the preparation of optically active hydroxyalkylated aziridines **7**, *diast*-**7**, **8** and *diast*-**8**, the stereochemistry of which has been deeply investigated by X-ray and NMR spectroscopic analyses to assign their absolute configurations. An interesting switch of the stereoselectivity, with reference to the newly created stereogenic centre, has been observed in the addition of *cis*-**1a**,**b-Li** to aromatic aldehydes depending on the substitution at the *ortho* position of the aromatic ring of the aldehyde. A model for the stereoselectivity observed in THF as been also proposed. A temperature-dependent regioselective lithiation has been demonstrated with aziridine (*S*,*S*)-**1c**. The lithiation performed at low temperature (−78 °C) furnished *ortho*-lithiated aziridine **1c-*ortho*-Li**, which reacted with electrophiles to furnish enantioenriched *ortho*-functionalised aziridines **10**. By performing the lithiation reaction at higher temperature (0 °C), the α-lithiated aziridine **1c-α-Li** formed almost exclusively and gave chiral non-racemic tri-substituted aziridines upon quenching with electrophiles. In summary, it has been demonstrated that just by finely tuning the reaction conditions it is possible to address the regio- and stereoselectivity of the lithiation/electrophile trapping sequence of two chiral parent aziridines, which can serve as an efficient preparation of highly enantioenriched functionalised aziridines.

Remarkably, the reductive ring-opening reactions of such functionalised aziridines furnished chiral amines, 1,2-, 1,3- and 1,5-aminoalcohols, and in some cases in both enantiomeric forms simply starting from the same parent aziridine. In addition, chiral aminoalkyl phthalans, which are useful building blocks in medicinal chemistry, could derive from *ortho*-hydroxyalkylated aziridines. Moreover, for the first time a configurationally stable aziridinyllithium (**1c**-α-**Li**) has been generated at relatively high temperature (0 °C),

thus paving the way for new applications of such reactive intermediates in organometallic chemistry.

Experimental Section

General: THF was freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. Petroleum ether refers to the 40–60 °C boiling fraction. For the ^{1}H and ^{13}C NMR spectra (^{1}H NMR: 400, 600 MHz; ^{13}C NMR: 150, 100 MHz), $CDCl_3$, CD_3OD and [D_8]toluene were used as the solvent. GC–MS spectrometry analyses were performed using a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Optical rotation values were measured using a polarimeter with a cell of 1 dm path length at 25 °C; the concentration (c) is expressed in g per 100 mL. Melting points were uncorrected. Analytical thin-layer chromatography (TLC) was carried out on pre-coated 0.25 mm thick plates of Kieselgel 60 F254; visualisation was accomplished by UV light (254 nm) or by spraying with a solution of 5% (w/v) ammonium molybdate and 0.2% (w/v) cerium(III) sulfate in 100 mL 17.6% (w/v) aq. sulfuric acid and heating to 473 K for some time until blue spots appeared. All reactions that involved air-sensitive reagents were performed under nitrogen in oven-dried glassware using a syringe/septum cap technique. Lithiation/electrophile trapping sequences were performed using a methanol/liquid N_2 (−84 °C) or acetone/dry ice (−78 °C) cold bath. The enantiomeric ratios were determined by HPLC analysis using a Daicel Chiralcel OD-H column (250×4.6 mm) or a Cellulose Lux-2 column (250×4.6 mm), and by ^{1}H NMR spectroscopy in the presence of Mosher's acid (1.5 equiv in $CDCl_3$).

General procedure for the lithiation-trapping sequence of aziridines (*S*,*S*)-1a,b in THF: *s*BuLi (1.5 mmol for **1a** and 2 mmol for **1b**, 1.4 M cyclohexane solution) was added dropwise to a solution of aziridine (*S*,*S*)-**1a** or (*S*,*S*)-**1b** (1 mmol) in dry THF (10 mL) at −78 °C under an N_2 atmosphere. The resulting brown mixture was stirred at −78 °C for the time indicated in Table 1 before adding the electrophile (neat if liquid or diluted in 2 mL of THF if solid). Then the reaction mixture was stirred at −78 °C until consumption of the starting aziridine (TLC-GC monitoring), warmed up to room temperature and quenched with a saturated solution of aq. NH_4Cl (3 mL). The resulting mixture was poured in water (20 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel (EtOAc/petroleum ether).

(2*R*,3*S*)-1-Benzyl-2-ethyl-2,3-diphenylaziridine (3b): Flash chromatography (petroleum ether/EtOAc 95:5), yellow solid, 91%. M.p. 77.8–78.2 °C; $[\alpha]_D^{20}=+35$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta=$ 7.51–753 (m, 2H; ArH), 7.30–7.36 (m, 2H; ArH), 7.21–7.25 (m, 1H; ArH), 6.96–7.11 (m, 10H; ArH), 4.27 (d, ^2J(H,H)=14.1 Hz, 1H; NC*H*H), 3.94 (d, ^2J(H,H)=14.1 Hz, 1H; NC*H*H), 2.86 (s, 1H; NCH), 2.25–2.35 (m, 1H; C*H*H), 1.93–2.02 (m, 1H; C*H*H), 0.88 ppm (t, ^3J(H,H)=7.4 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta=$ 140.3, 139.5, 138.2, 129.3, 128.2, 128.0, 127.3, 127.2, 126.7, 126.0[2], 126.0, 56.3, 56.1, 53.5, 25.9, 11.3 ppm; IR (KBr): $\tilde{\nu}=$698, 733, 754, 1028, 1073, 1125, 1356, 1452, 1495, 1602, 2875, 2965, 3027, 3060 cm^{-1}; MS (70 eV): m/z (%): 313 (4) [M^+], 312 (3) [M^+-H], 223 (18), 222 (100) [$M^+-C_7H_7$], 194 (7), 167 (16), 165 (9), 115 (7), 91 (33) [$C_7H_7^+$]; elemental analysis calcd (%) for $C_{23}H_{23}N$: C 88.13, N 4.47, H 7.40; found: C 87.75, N 4.51, H 7.37; enantiomeric purity (e.r.>98:2) ascertained by ^{1}H NMR spectroscopy in the presence of Mosher's acid (see the Supporting Information).

(1*R*,2′*R*,3′*S*)-(2,3-Diphenyl-1-propylaziridin-2-yl)phenylmethanol (8a): Flash chromatography (petroleum ether/EtOAc 90:10), white solid, 68%. M.p. 89.8–90.2 °C; $[\alpha]_D^{20}=+42$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta=$7.16–7.28 (m, 5H; ArH), 6.86–7.04 (m, 8H; ArH), 6.54 (d, ^3J(H,H)=7.3 Hz, 2H; ArH), 5.13 (d, ^3J(H,H)=7.3 Hz, 1H; *CH*OH), 3.41–3.47 (m, 1H; NC*H*H), 3.17 (s, 1H; NCH), 2.82–2.88 (m, 1H; NC*H*H), 2.00 (d, ^3J(H,H)=7.3 Hz, 1H; OH), 1.76–1.88 (m, 2H; CH_3CH_2), 1.05 ppm (t, ^3J(H,H)=7.4 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta=$142.4, 137.5, 134.5, 131.7, 128.2, 127.6, 127.5, 127.4, 126.93, 126.91, 126.6, 126.4, 74.3, 58.9, 55.5, 52.8, 24.0, 12.4 ppm; IR (KBr): $\tilde{\nu}=$698, 760, 784, 846, 915, 940, 1008, 1047, 1076, 1200, 1250, 1403, 1455, 1495, 1603, 2869, 2932, 2962, 3029, 3056, 3429 cm^{-1}; ESI-MS: m/z (%): 344 (100) [M+H]$^+$; elemental analysis calcd (%) for $C_{24}H_{25}NO$: C 83.93, N 4.08, H 7.34; found: C 83.73, N 4.21, H 7.31; enantiomeric purity (e.r.>98:2) ascertained by ^{1}H NMR spectroscopy in the presence of Mosher's acid (see the Supporting Information).

General procedure for the lithiation–trapping sequence of aziridines (*S*,*S*)-1a,b in toluene: *s*BuLi (1.5 mmol for **1a** and 2 mmol for **1b**, 1.4 M cyclohexane solution) was added dropwise to a solution of aziridine (*S*,*S*)-**1a** or (*S*,*S*)-**1b** (1 mmol) and TMEDA (1.5 mmol for **1a** and 2 mmol for **1b**) in dry toluene (10 mL) at the temperature indicated in Table 1 and under an N_2 atmosphere. The resulting brown mixture was stirred for the time reported in Table 1 and the electrophile was added (neat if liquid or diluted in toluene (2 mL) if solid). Stirring was continued at the reported temperature until consumption of the starting aziridine (TLC-GC monitoring), then the mixture was warmed up to room temperature and quenched with a saturated solution of aq. NH_4Cl (3 mL). The mixture was poured into water (20 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel (EtOAc/petroleum ether).

(2*S*,3*S*)-1-Benzyl-2-ethyl-2,3-diphenylaziridine (4b): Flash chromatography (petroleum ether/EtOAc 95:5), yellow oil, 68%. $[\alpha]_D^{20}=-14$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta=$7.38–7.40 (m, 2H; ArH), 7.32–7.35 (m, 2H; ArH), 7.20–7.30 (m, 7H; ArH), 7.07–7.16 (m, 4H; ArH), 3.64 (d, ^2J(H,H)=14.1 Hz, 1H; NC*H*H), 3.14 (s, 1H; NCH), 2.92 (d, ^2J(H,H)=14.1 Hz, 1H; NC*H*H), 1.82–1.91 (m, 1H; CH_3CHH), 1.26–1.35 (m, 1H; CH_3CHH), 0.34 ppm (t, ^3J(H,H)=7.4 Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta=$140.0, 138.2, 137.8, 130.5, 128.12, 128.1, 127.9, 127.84, 127.8, 127.5, 126.6, 126.5, 58.9, 56.7, 51.2, 28.4, 9.5 ppm; IR (film): $\tilde{\nu}=$698, 800, 868, 1027, 1074, 1096, 1261, 1399, 1455, 1495, 1602, 2964, 3027, 3062 cm^{-1}; MS (70 eV): m/z (%): 313 (4) [M^+], 312 (4) [M^+-H], 223 (18), 222 (100) [$M^+-C_7H_7$], 194 (13), 167 (17), 165 (9), 115 (7), 91 (44) [$C_7H_7^+$]; enantiomeric purity (e.r.>98:2) ascertained by ^{1}H NMR spectroscopy in the presence of Mosher's acid (see the Supporting Information).

(1*S*,2′*S*,3′*S*)-(2,3-Diphenyl-1-propylaziridin-2-yl)phenylmethanol (7a): Flash chromatography (petroleum ether/EtOAc 95:5), white solid, 38%. M.p. 114.6–115.0 °C; $[\alpha]_D^{20}=-4$ ($c=1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, D_2O exchange, 298 K): $\delta=$7.55 (d, ^3J(H,H)=7.3 Hz, 2H; ArH); 7.41 (t, ^3J(H,H)=7.7 Hz, 2H; ArH), 7.17–7.34 (m, 6H; ArH), 6.87–6.97 (m, 3H; ArH), 6.40 (d, ^3J=6.4 Hz, 2H; ArH), 4.42 (s, 1H; *CH*OH), 3.15 (s, 1H; NCH), 2.86–2.91 (m, 1H; C*H*H), 1.63–1.76 (m, 2H; CH_2), 1.51–1.61 (m, 1H; C*H*H), 0.90 ppm (t, ^3J(H,H)=7.2 Hz, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): $\delta=$139.9, 137.4, 134.4, 131.7, 128.2, 127.9, 127.5, 127.3, 127.2, 127.1, 126.6, 126.0, 75.4, 59.8, 57.9, 53.5, 23.3, 12.0 ppm; IR (KBr): $\tilde{\nu}=$700, 714, 766, 1043, 1450, 1495, 1602, 2836, 2861, 2926, 2955, 3057, 3481 cm^{-1}; ESI-MS: m/z (%): 344 (100) [M+H]$^+$; elemental analysis calcd (%) for $C_{24}H_{25}NO$: C 83.93, N 4.08, H 7.34; found: C 83.66, N 4.07, H 7.30; enantiomeric purity (e.r.>98:2) ascertained by ^{1}H NMR spectroscopy in the presence of Mosher's acid (see the Supporting Information).

(1*R*,2′*S*,3′*S*)-(2,3-Diphenyl-1-propylaziridin-2-yl)phenylmethanol (*diast*-7a): Flash chromatography (petroleum ether/EtOAc 95:5), colourless oil, 39%. $[\alpha]_D^{20}=-12$ ($c=1$ in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, 298 K): $\delta=$7.55 (d, ^3J=7.1 Hz, 2H; ArH), 7.37 (t, ^3J(H,H)=7.2 Hz, 2H; ArH), 7.28–7.33 (m, 4H; ArH), 7.09–7.20 (m, 5H; ArH), 6.94 (d, ^3J(H,H)= 7.1 Hz, 2H; ArH), 4.69 (s, 1H; *CH*OH), 3.12 (s, 1H; NCH), 2.73–2.76 (m, 1H; NC*H*H), 1.55–1.73 (m, 3H; CH_3CH_2 and NC*H*H), 0.99 ppm (t, ^3J(H,H)=7.1 Hz, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): $\delta=$ 141.2, 137.1, 135.1, 132.0, 128.1, 127.9, 127.7, 127.3, 127.0, 126.7, 126.2, 74.6, 59.0, 56.7, 51.5, 23.3, 12.1 ppm; IR (film): $\tilde{\nu}=$703, 712, 754, 1027, 1044, 1072, 1110, 1198, 1242, 1376, 1448, 1495, 1601, 2849, 2872, 2931, 2958, 3028, 3058, 3469 cm^{-1}; ESI-MS: m/z (%): 344 (100) [M+H]$^+$; HRMS: m/z: calcd for $C_{24}H_{26}NO$ [M+H]$^+$: 344.2014; found: 344.2019.

Enantiomeric purity (e.r. > 98:2) ascertained by ^{1}H NMR spectroscopy in the presence of Mosher's acid (see the Supporting Information).

General procedure for the lithiation–trapping sequence of aziridines (*S*,*S*)-1c at 0 °C: *s*BuLi (1.5 mmol, 1.4 M cyclohexane solution) was added dropwise to a solution of aziridine (1 mmol) and TMEDA (1.5 mmol) in Et_2O (10 mL) at 0 °C and under an N_2 atmosphere. The resulting orange mixture was stirred for 3.5 h before adding the electrophile (neat if liquid or diluted in 2 mL of Et_2O if solid). Then a solution of sat. aq. NH_4Cl (3 mL) was added and the mixture poured into water (20 mL) and extracted with Et_2O (3×10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel (EtOAc/petroleum ether).

(2*R*,3*S*)-1,3-Dimethyl-2-trimethylsilyl-2-phenylaziridine (*cis*-5c): Flash chromatography (petroleum ether/EtOAc 40:60), colourless oil, 65%. $[\alpha]_D^{20} = -66$ ($c = 1$, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 7.17$–7.21 (m, 2H; ArH); 7.06–7.11 (m, 3H; ArH), 2.74 (s, 3H; NCH_3), 1.88 (q, $^3J(H,H) = 5.6$ Hz, 1H; $CHCH_3$), 0.92 (d, $^3J(H,H) = 5.6$ Hz, 3H; $CHCH_3$), 0.03 ppm (s, 9H; $3\times CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 141.6$, 129.4, 127.5, 125.3, 44.4, 43.5, 16.2, 0.2 ppm; IR (film): $\tilde{\nu} = 702$, 837, 884, 1249, 1453, 1488, 2952, 3024, 3056 cm^{-1}; MS (70 eV): *m*/*z* (%): 219 (24) [M^+], 218 (100) [M^+-H], 204 (14), 135 (18), 105 (27), 73 (37). Enantiomeric purity determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/*i*PrOH 99:1, flow rate 0.4 mL min^{-1}, $\lambda = 220$ nm; for racemic aziridine, $t_1 = 10.33$ min, $t_2 = 10.85$ min; for enantioenriched aziridine, $t = 10.49$ min).

(1*R*,2′*S*,3′*S*)-4-Chlorophenyl-(1,3-dimethyl-2-phenylaziridin-2-yl)methanol (9c): Flash chromatography (petroleum ether/EtOAc 80:20), white solid, 35%. M.p. 113.0–114.0 °C; $[\alpha]_D^{20} = +22$ ($c = 0.9$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): $\delta = 7.32$–7.33 (m, 3H; ArH), 7.14–71.5 (m, 4H; ArH), 7.01 (d, $^3J(H,H) = 8.3$ Hz, 2H; ArH), 5.07 (s, 1H; *CH*OH), 2.13 (s, 3H; NCH), 2.00 (q, $^3J(H,H) = 6.0$ Hz, 1H; $CHCH_3$), 1.35 ppm (d, $^3J(H,H) = 6.0$ Hz, 3H; $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta =$ 139.8, 136.7, 132.4, 131.6, 128.2, 128.1, 127.7, 74.2, 54.8, 45.2, 40.9, 14.0 ppm; IR (KBr): $\tilde{\nu} = 704$, 730, 828, 1014, 1075, 1090, 1131, 1405, 1446, 1490, 2870, 2924, 2956, 3059, 3368 cm^{-1}; ESI-MS: *m*/*z* (%): 288 (100) [$M-H]^+$; elemental analysis calcd (%) for $C_{17}H_{18}ClNO$: C 70.95, N 4.87, H 6.30; found: C 70.54, N 4.85, H 6.28. Enantiomeric purity determined by HPLC analysis (Cellulose Lux-2, hexane/*i*PrOH 90:10, flow rate 0.8 mL min^{-1}, $\lambda = 260$ nm; for racemic aziridine, $t_1 = 6.13$ min, $t_2 =$ 7.18 min; for enantioenriched aziridine, $t = 6.17$ min).

(1*S*,2′*S*,3′*S*)-4-Chlorophenyl-(1,3-dimethyl-2-phenylaziridin-2-yl)methanol (*diast*-9c): Flash chromatography (petroleum ether/EtOAc 80:20),white solid, 35%. M.p. 184.0–185.0 °C; $[\alpha]_D^{20} = +39$ ($c = 1.9$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): $\delta = 7.19$–7.28 (m, 5H; ArH), 7.11 (d, $^3J(H,H) = 8.4$ Hz, 2H; ArH), 6.99 (d, $^3J(H,H) = 8.4$ Hz, 2H; ArH), 5.95 (br s, 1H; OH), 4.83 (s, 1H; *CH*OH), 2.27 (s, 3H; NCH_3), 2.07 (q, $^3J(H,H) = 6.0$ Hz, 1H; $CHCH_3$), 1.64 ppm (d, $^3J(H,H) = 6.0$, 3H; $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta = 140.1$, 134.5, 132.3, 132.0, 127.7, 127.5, 127.4, 74.3, 56.9, 47.2, 42.2, 14.6 ppm; IR (KBr): $\tilde{\nu} =$ 704, 730, 1014, 1050, 1066, 1090, 1404, 1447, 1490, 2852, 2921, 2955, 3086 cm^{-1}; ESI-MS: *m*/*z* (%): 288 (100) [$M+H]^+$; elemental analysis calcd (%) for $C_{17}H_{18}ClNO$: C 70.95, N 4.87, H 6.30; found: C 70.54, N 4.85, H 6.28. Enantiomeric purity determined by HPLC analysis (Cellulose Lux-2, hexane/*i*PrOH 90:10, flow rate 0.8 mL min^{-1}, $\lambda = 260$ nm; for racemic aziridine, $t_1 = 6.53$ min, $t_2 = 7.01$ min; for enantioenriched aziridine, $t = 6.94$ min).

General procedure for the lithiation–trapping sequence of aziridines (*S*,*S*)-1c at −78 °C: *s*BuLi (1.5 mmol of a 1.4 M cyclohexane solution) was added dropwise to a solution of aziridine (1 mmol) in dry THF (10 mL) at −78 °C and under an N_2 atmosphere. The resulting brown mixture was stirred for 4 h before adding the electrophile (neat if liquid or diluted in 2 mL of THF if solid). The mixture was stirred at −78 °C until consumption of the starting aziridine (TLC-GC monitoring) and then warmed up to room temperature. A solution of sat. aq. NH_4Cl (3 mL) was added, the mixture poured into water (20 mL), and then extracted with Et_2O (3× 10 mL). The combined organic layers were dried (Na_2SO_4) and the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel (EtOAc/petroleum ether) or by crystallisation.

(2*S*,3*S*)-1,2-Dimethyl-3-(2-trimethylsilylphenyl)aziridine (6c): Flash chromatography (petroleum ether/EtOAc 95:5), colourless oil, 88% as inseparable mixture of invertomers (d.r. = 83:17, $CDCl_3$, 263 K). $[\alpha]_D^{20} = +70$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 263 K): $\delta = 7.57$ (d, $^3J(H,H) = 7.0$ Hz, 1H, minor; ArH), 7.46 (d, $^3J(H,H) = 7.2$ Hz, 1H, major; ArH), 7.29–7.35 (m, 1 H major + 2 H minor; ArH), 7.18–7.21 (m, 2H, major; ArH), 7.14 (d, $^3J(H,H) = 7.0$ Hz, 1H, minor; ArH), 2.96 (d, $^3J(H,H) = 2.9$ Hz, 1H, minor; Ar*CH*N), 2.56 (s, 3H, major; NCH_3), 2.28 (d, $^3J(H,H) = 2.8$ Hz, 1H, major; Ar*CH*N), 2.17–2.21 (m, 1H, minor; N*CH*CH_3), 2.03–2.06 (m, 1H, major; N*CH*CH_3), 2.01 (s, 3H, minor; NCH_3), 1.39 (d, $^3J(H,H) = 5.8$ Hz, 3H, major; $CHCH_3$), 1.34 (d, $^3J(H,H) = 5.3$ Hz, 3H, minor; $CHCH_3$), 0.40 (s, 9H, minor; $3\times CH_3$), 0.36 ppm (s, 9H, major; $3\times CH_3$); ^{13}C NMR (spectra description for the major invertomer, 150 MHz, $CDCl_3$, 263 K): $\delta = 145.9$, 137.5, 133.8, 129.6, 125.7, 123.7, 49.4, 43.5, 38.4, 11.0, 0.4 ppm; IR (film): $\tilde{\nu} = 620$, 741, 837, 1087, 1121, 1249, 1398, 1438, 1466, 2955, 3053 cm^{-1}; MS (70 eV): *m*/*z* (%): 219 (19) [M^+], 218 (81) [M^+-H], 205 (15), 204 (87), 147 (16), 146 (100) [M^+-SiCH_3], 145 (24), 144 (14), 131 (19), 73 (41) [$SiCH_3^+$]; ESI-MS: *m*/*z* (%): 220 (100) [$M+H]^+$. Enantiomeric purity (e.r. > 98:2) ascertained by ^{1}H NMR spectroscopy in the presence of Mosher's acid (see the Supporting Information).

(1*R*,2′*S*,3′*S*)-4-Chlorophenyl-[2-(1,3-dimethylaziridin-2-yl)phenyl]methanol (*diast*-10c): Flash chromatography (petroleum ether/EtOAc 20:80), colourless oil, 23% as inseparable mixture of invertomers (d.r. = 87:13, $CDCl_3$, 298 K). $[\alpha]_D^{20} = +99$ ($c = 2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 7.17$–7.29 (m, 8H, major; ArH), 7.07–7.16 (m, 7H, minor; ArH), 6.87–6.89 (m, 1H, minor; ArH), 6.17 (s, 1H, minor; *CH*OH), 5.60 (s, 1H, major; *CH*OH), 3.28 (d, $^3J(H,H) = 4.0$ Hz, 1H, minor; ArCHN), 2.04 (d, $^3J(H,H) = 3.3$ Hz, 1H, major; ArCHN), 1.94–2.00 (m, 1H major + 1H minor; $2\times CH_3CHN$), 1.90 (s, 3H, major; NCH_3), 1.67 (s, 3H, minor; NCH_3), 1.31 (d, $^3J(H,H) = 4.4$ Hz, 3H, minor; $CHCH_3$), 1.20 ppm (d, $^3J(H,H) = 6.0$ Hz, 3H, major; $CHCH_3$); ^{13}C NMR (spectra description for both the invertomers, 100 MHz, $CDCl_3$, 298 K): $\delta = 143.3$, 142.3, 140.9, 138.3, 137.9, 132.5, 130.0, 129.45, 129.4, 128.7, 128.2, 128.1, 127.94, 127.92, 127.8, 127.1, 122.3, 121.3, 84.4, 84.2, 75.8, 57.8, 48.6, 39.9, 36.7, 29.7, 14.6, 10.9 ppm; IR (film): $\tilde{\nu} = 759$, 1013, 1032, 1088, 1171, 1263, 1377, 1402, 1457, 1488, 1601, 2850, 2920, 2957, 3413 cm^{-1}; ESI-MS: *m*/*z* (%): 288 (100) [$M+H]^+$.

(1*S*,2′*S*,3′*S*)-4-Chlorophenyl-[2-(1,3-dimethylaziridin-2-yl)phenyl]methanol (10c): Flash chromatography (petroleum ether/EtOAc 20:80), white solid, 28% as inseparable mixture of invertomers (d.r. = 77:23, $CDCl_3$, 298 K). M.p. 140.0–141.0 °C; $[\alpha]_D^{20} = +23$ ($c = 1.2$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 7.10$–7.35 (m, 15H, major + minor; ArH), 7.03–7.06 (m, 1H, major; ArH), 6.08 (s, 1H, major; *CH*OH), 5.86 (s, 1H, minor; *CH*OH), 2.78 (d, $^3J(H,H) = 3.7$ Hz, 1H, minor; Ar*CH*N), 2.54 (s, 3H, major; NCH_3), 2.31 (d, $^3J(H,H) = 3.3$ Hz, 1H, major; Ar*CH*N), 2.08 (s, 3H, minor; NCH_3), 2.00–2.06 (m, 1H major + 1H minor; N*CH*CH_3), 1.38 (d, $^3J(H,H) = 5.5$ Hz, 3H, minor; $CHCH_3$), 1.32 ppm (d, $^3J(H,H) =$ 6.0 Hz, 3H, major; $CHCH_3$); ^{13}C NMR (spectra description for both the invertomers, 100 MHz, $CDCl_3$, 298 K): $\delta = 145.2$, 143.3, 143.2, 141.1, 137.6, 132.8, 132.6, 130.5, 130.1, 128.6, 128.4, 128.3, 128.2, 128.1, 127.8, 127.5, 127.3, 127.24, 127.2, 126.8, 71.9, 69.8, 48.1, 45.6, 40.8, 39.1, 39.0, 37.8, 17.6, 10.8 ppm; ESI-MS: *m*/*z* (%): 288 (100) [$M+H]^+$; IR (KBr): $\tilde{\nu} = 759$, 1014, 1033, 1089, 1457, 1488, 2850, 2920, 3420 cm^{-1}. Enantiomeric purity determined by HPLC analysis (Cellulose Lux-2, hexane/*i*PrOH 90:10, flow rate 0.8 mL min^{-1}, $\lambda = 260$ nm; for racemic aziridine, $t_1 =$ 10.53 min, $t_2 = 15.42$ min; for enantioenriched aziridine, t = 10.42 min).

General procedure for the reductive ring-opening of substituted aziridines: $Pd(OH)_2$ (20 mol%) was added to a solution of aziridine (1 mmol) in EtOAc or MeOH (1 mL). The mixture was connected with a cannula to a balloon filled with hydrogen at room temperature and stirred until consumption of the starting aziridine (TLC-GC monitoring). The reaction mixture was filtered on a celite pad and concentrated in vacuo. The crude was purified by chromatography on silica gel or by crystallisation.

(*R*)-1,2-Diphenyl-*N*-propylbutan-2-amine (11a): Flash chromatography (petroleum ether/EtOAc, 90:10), pale yellow oil, 81%. $[\alpha]_D^{20} = +14$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): $\delta = 7.23$–7.29 (m, 4H; ArH), 7.16–7.19 (m, 1H; ArH), 7.09–7.10 (m, 3H; ArH), 6.70–6.72 (m,

2H; ArH), 2.97 (s, 2H; $ArCH_2$), 2.30–2.41 (m, 2H; NCH_2), 1.66–1.81 (m, 2H; CH_2), 1.40–1.49 (m, 2H; CH_2), 0.89 (t, $^3J(H,H)=7.4$ Hz, 3H; CH_3), 0.83 ppm (t, $^3J(H,H)=7.3$ Hz, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): $\delta=145.5$, 137.7, 130.3, 127.7, 126.6, 127.1, 126.0, 125.95, 61.8, 43.9, 43.7, 28.5, 23.8, 12.0, 7.8 ppm; IR (film): $\tilde{\nu}=703$, 751, 765, 1030, 1075, 1151, 1379, 1455, 1496, 1599, 2872, 2927, 2962, 3024, 3052, 3080, 3336 cm^{-1}; ESI-MS: *m/z* (%): 268 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{25}N\cdot HCl$: C 75.10, N 4.61, H 8.62; found: C 75.41, N 4.67, H 8.57. Enantiomeric purity determined by HPLC analysis (Cellulose Lux-2, hexane/*i*PrOH 99.5:0.5, flow rate 0.6 mL min^{-1}, $\lambda=260$ nm; for racemic amine, $t_1=5.75$ min, $t_2=6.00$ min; for enantioenriched amine, $t=5.77$ min).

(*S*)-1,2-Diphenyl-*N*-propylbutan-2-amine (*ent*-11a): Colourless oil, 55%. $[\alpha]_D^{20}=-14$ ($c=1$ in $CHCl_3$). Enantiomeric purity was determined by HPLC analysis (Cellulose Lux-2, hexane/*i*PrOH 99.8:0.2, flow rate 1.0 mL min^{-1}, $\lambda=260$ nm; for racemic amine, $t_1=4.50$ min, $t_2=5.50$ min; for enantioenriched amine, $t=5.54$ min).

(1*R*,2*S*)-1,2,3-Triphenyl-2-(propylamino)propan-1-ol (*ent*-13): Flash chromatography (hexane/CH_2Cl_2 30:70), white oil, 65%. $[\alpha]_D^{20}=+70$ ($c=0.5$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 298 K): $\delta=7.02$–7.27 (m, 13H; ArH), 6.81 (d, $^3J(H,H)=7.4$ Hz, 2H; ArH), 4.88 (s, 1H; *CH*OH), 3.27–3.39 (2×d, AB system, $^2J(H,H)=15.1$ Hz, 2H; $ArCH_2$), 2.69–2.78 (m, 2H; NCH_2), 1.38–1.55 (m, 2H; CH_2), 0.92 ppm (t, $^3J(H,H)=7.3$ Hz, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta=139.8$, 139.3, 137.0, 130.1, 128.9, 128.4, 128.2, 127.4, 127.1, 127.05, 126.9, 126.4, 76.9, 66.2, 43.2, 37.4, 23.7, 11.8 ppm; IR (KBr): $\tilde{\nu}=700$, 1032, 1051, 1263, 1396, 1453, 1495, 1602, 2873, 2929, 2960, 3029, 3060, 3087, 3400 cm^{-1}; ESI-MS: *m/z* (%): 346 (100) $[M+H]^+$.

(1*S*,2*R*)-1,2,3-Triphenyl-2-(propylamino)propan-1-ol (13): $[\alpha]_D^{20}=-74$ ($c=0.5$ in $CHCl_3$). Enantiomeric purity of **13** and *ent*-**13** was determined by HPLC analysis (Cellulose Lux-2, hexane/*i*PrOH 95:5, flow rate 1.0 mL min^{-1}, $\lambda=260$ nm; for racemic amino alcohol, $t_1=6.09$ min, $t_2=9.49$ min; for *ent*-**13**, $t=5.98$ min; for **13**, $t=9.45$).

(1*S*,2*R*,3*S*)-3-(Methylamino)-1,2-diphenylbutan-1-ol (14c): Crystallised from Et_2O, white solid, 70%. M.p. 194.5–195.0 °C; $[\alpha]_D^{20}=-48.5$ ($c=0.2$ in $EtOH_{(abs)}$); ^1H NMR (400 MHz, CD_3OD, 298 K): $\delta=7.18$ (brs, 5H; ArH), 7.02–7.09 (m, 5H; ArH), 5.34 (d, $^3J(H,H)=3.6$ Hz, 1H; Ar*CH*OH), 3.91 (quintet, $^3J(H,H)=6.6$ Hz, 1H; CH_3CHCH), 3.06 (dd, $^3J(H,H)=6.6$, 3.6 Hz, 1H; Ar*CH*), 2.61 (s, 3H; NCH_3), 1.50 ppm (dd, $^3J(H,H)=6.6$ Hz, 3H; $CHCH_3$); ^{13}C NMR (100 MHz, CD_3OD, 298 K): $\delta=142.6$, 134.3, 130.4, 128.0, 127.4, 127.2, 126.5, 125.5, 74.0, 58.6, 55.1, 30.0, 13.7 ppm; IR (KBr): $\tilde{\nu}=704$, 1057, 1453, 1602, 2851, 2924, 3028, 3350 cm^{-1}; ESI-MS: *m/z* (%): 256 (100) $[M+H]^+$; elemental analysis calcd (%) for $C_{17}H_{21}NO\cdot HCl$: C 69.97, N 4.80, H 7.60; found: C 70.11, N 5.15, H 8.02. Enantiomeric purity determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/*i*PrOH 95:5, flow rate 0.8 mL min^{-1}, $\lambda=210$ nm; for racemic amino alcohol, $t_1=15.67$ min, $t_2=19.41$ min; for enantioenriched amino alcohol, $t=19.70$ min).

(*S*)-2-[2-(methylamino)propylphenyl]diphenylmethanol (15): Flash chromatography (EtOAc), white solid, 75%. M.p. 124.0–125.0 °C; $[\alpha]_D^{20}=+143.3$ ($c=1.3$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 298 K): $\delta=7.18$–7.30 (m, 12H; ArH), 6.97–7.02 (m, 1H; ArH), 6.62 (d, $^3J(H,H)=7.8$ Hz, 1H; ArH), 2.71–2.79 (m, 1H; $NCHCH_3$), 2.65 (dd, $^{2,3}J(H,H)=13.3$, 9.1 Hz, 1H; ArC*H*H), 2.50 (dd, $^{2,3}J(H,H)=13.3$, 4.0 Hz, 1H; ArC*H*H), 2.05 (s, 3H; NCH_3), 1.10 ppm (d, $^3J(H,H)=6.4$ Hz, 3H; $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta=149.8$, 148.9, 147.1, 139.0, 132.1, 130.4, 128.2, 127.5, 127.48, 127.46, 127.4, 126.3, 126.2, 125.3, 81.2, 56.7, 42.1, 34.7, 21.1 ppm; IR (KBr): $\tilde{\nu}=701$, 759, 1036, 1445, 1486, 2797, 2962, 3021, 3056, 3306 cm^{-1}; MS (70 eV): *m/z* (%): 331 (5) $[M^+]$, 313 (3) $[M^+-H_2O]$, 298 (6), 254 (9), 236 (39), 178 (12), 165 (8), 77 (8), 58 (100); elemental analysis calcd (%) for $C_{23}H_{25}NO$: C 83.34, N 4.23, H 7.60; found: C 83.22, N 4.26, H 7.57.

General procedure for the synthesis of aminoalkylphthalans: A solution of *ortho*-hydroxyalkylated phenylaziridine **10** (1 mmol) in acetic acid (3.0 mL) was stirred at room temperature until the substrate disappeared (TLC-GC monitoring). The reaction mixture was poured into aq. NaOH (20 mL, 10%), extracted with CH_2Cl_2 (3×10 mL), dried (Na_2SO_4), and concentrated in vacuo. The crude reaction mixture was purified by flash chromatography.

(1*R*,1′*S*)-3,3-Diphenyl-1-(methylaminoethyl)-1,3-dihydroisobenzofuran (16a): Flash chromatography (CH_2Cl_2/MeOH 95:5), yellow oil, 76%. $[\alpha]_D^{20}=+19$ ($c=1$ in $CHCl_3$); ^1H NMR (600 MHz, $CDCl_3$, 298 K): $\delta=7.40$ (d, $J=7.6$ Hz, 2H; ArH), 7.20–7.31 (m, 12H; ArH), 5.46 (d, $^3J=2.0$ Hz, 1H; Ar*CH*O), 3.11–3.13 (m, 1H; N*CH*CH_3), 2.51 (s, 3H; NCH_3), 0.97 ppm (d, $^3J(H,H)=6.5$ Hz, 3H; $CHCH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, 298 K): $\delta=145.0$, 144.9, 144.8, 140.4, 127.91, 127.9, 127.8, 127.7, 127.5, 127.4, 127.0, 126.7, 123.9, 121.5, 92.1, 83.5, 57.8, 33.7, 14.5 ppm; IR (film): $\tilde{\nu}=699$, 758, 999, 1446, 1490, 2796, 2874, 2969, 3026, 3058, 3326 cm^{-1}; ESI-MS: *m/z* (%): 330 (100) $[M+H]^+$. Enantiomeric purity (e.r. > 98:2) ascertained by ^1H NMR spectroscopy in the presence of Mosher's acid (see the Supporting Information).

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tion, (see ref. [8]). It is worth pointing out that the same solvent-dependent reactivity has been observed with *N*-benzylaziridine (*S*,*S*)-**1b**, reported here for the first time.

[12] The reaction needs to be performed in Et_2O to avoid the competitive deprotonation of THF under these conditions. However, it has been demonstrated that the solvent does not affect the regioselectivity (see ref. [6]).

[13] The retention of configuration has been demonstrated by NOESY experiments on derivatives **5** (see the Supporting Information).

[14] A reported solvent-dependent *ortho*/α-benzylic competition showed that the *ortho* position is kinetically favoured, see: M. Linnert, C. Bruhn, T. Ruffer, H. Schmidt, D. Steinborn, *Organometallics* **2004**, *23*, 3668–3673.

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[18] The retention of configuration and preservation of the enantiomeric purity have been demonstrated on both diastereoisomers **7** and *diast*-**7** by comparison of spectral data with that of known compounds, by NOESY experiments and by analysis of the enantiomeric composition against a racemic sample.

[19] It is worth pointing out that in the case of the 2-furyl substituent, the absolute configuration should be (*S*,*S*,*R*) for **7b** and (*S*,*S*,*S*) for *diast*-**7b** because of a change in the priority order of the 2-furyl group.

[20] The X-ray analysis furnished either relative or absolute configuration of hydroxyalkyl derivatives **8a**,**d** and *diast*-**8e**,**f**. See the Supporting Information.

[21] Attempts to isolate an analytically pure sample of the minor isomer failed.

[22] This interesting phenomenon could allow the establishment of some C–C bond rotation barriers and is currently under investigation by dynamic NMR spectroscopy. The results will be reported in due course.

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[24] These assignments seem to be the better choice in terms of fitting with the observed stereochemistry.

[25] It cannot be ruled out that a different stability of the products **8** and *diast*-**8** could be responsible for the stereoselectivity switch. Nevertheless, it could be also considered that the *ortho*-substituent on the aromatic ring of the aldehyde could induce a steric inhibition of resonance, thereby giving a non-planar conformer and thus favouring complex B. For a recent paper on this possibility, see: D. Hnyk, S. Samdal, O. Exner, D. A. Wann, D. W. H. Rankin, *J. Org. Chem.* **2010**, *75*, 4939–4943. The irreversibility of the addition reaction has been also verified by quenching the reaction between *cis*-**1a-Li** and benzaldehyde at short (5 min) and long (2 h) reaction times. In both experiments, the same diastereomeric ratio has been observed (90:10). See Table 3.

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[28] The lower yields that were observed when starting from *trans*-aziridines **4** should be ascribed to a competing ring opening that involves the more substituted benzylic carbon.

[29] The enantiomeric relationship between amines **11a–d** and *ent*-**11a–d** was demonstrated on the basis of chiral HPLC analyses and the values of optical rotation. It was also verified that no loss of optical purity occurred during the lithiation/trapping/reduction sequence (see the Supporting Information).

[30] The enantiomeric relationship between **13** and *ent*-**13** has been demonstrated by chiral HPLC analysis (see the Supporting Information).

[31] It is worth pointing out that X-ray analysis provided the configuration of **8a** and **7a** but not for *diast*-**7a**.

[32] For recent syntheses of phthalans and phthalides, their pharmacological activity, and their usefulness as intermediates in the preparation of other bioactive compounds, see: a) J. F. DeBernardis, D. L. Arendsen, J. J. Kyncl, D. J. Kerkman, *J. Med. Chem.* **1987**, *30*, 178–184; b) S. Zemolka, J. Lex, H.-G. Schmalz, *Angew. Chem.* **2002**, *114*, 2635–2638; *Angew. Chem. Int. Ed.* **2002**, *41*, 2525–2528; c) M. Yus, F. Foubelo, J. V. Ferrández, *Tetrahedron* **2003**, *59*, 2083–2092; d) M. A. Yurovskaya, *Chem. Heterocycl. Compd.* **2005**, *41*, 24–78.

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