Solvent- and Temperature-Dependent Functionalisation of Enantioenriched Aziridines


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 aziridinyl-lithiums 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 oxiranylolithiums, 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-
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.

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 could affect the stereoselectivity of the lithiation/trapping sequence of trans-N-alkyl-2,3-diphenylaziridines. [7]

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

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 co-workers. [8] Reaction of hydrobenzoin with SOCl2 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 nBuLi (Scheme 3).

Chiral N-methyl-2-phenylaziridine (S,S)-1c could be prepared from commercially available (+)-ephedrine by cyclisation under Mitsunobu conditions (Scheme 3). [9]

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 sBuLi 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

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**Scheme 1.** Dynamically controlled reactivity.

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

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

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>T [°C]</th>
<th>t [h]</th>
<th>E Yield [%][a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>nPr</td>
<td>−78</td>
<td>3</td>
<td>Et 92[b]</td>
</tr>
<tr>
<td>4a</td>
<td>nPr</td>
<td>−78</td>
<td>4</td>
<td>Et 95[h]</td>
</tr>
<tr>
<td>3b</td>
<td>Bn</td>
<td>−78</td>
<td>1.5</td>
<td>Et 91[h]</td>
</tr>
<tr>
<td>4b</td>
<td>Bn</td>
<td>−84</td>
<td>1</td>
<td>Et 68[h]</td>
</tr>
<tr>
<td>3c</td>
<td>nPr</td>
<td>−78</td>
<td>3</td>
<td>Me 98[i]</td>
</tr>
<tr>
<td>4c</td>
<td>nPr</td>
<td>−78</td>
<td>4</td>
<td>Me 64[i]</td>
</tr>
<tr>
<td>3d</td>
<td>Bn</td>
<td>−78</td>
<td>1.5</td>
<td>nPr 90[i]</td>
</tr>
<tr>
<td>4d</td>
<td>Bn</td>
<td>−84</td>
<td>1</td>
<td>nPr 78[i]</td>
</tr>
<tr>
<td>3e</td>
<td>Bn</td>
<td>−78</td>
<td>1.5</td>
<td>SiMe3 50[j]</td>
</tr>
</tbody>
</table>

[a] Isolated yields. [b] Enantiomeric ratios ascertained by 1H NMR spectroscopy (see the Supporting Information). [c] Enantiomeric ratios were assigned by analogy; no epimerisation was detected by 1H NMR spectroscopy (see the Supporting Information). [d] Enantiomeric ratios were ascertained by 1H NMR spectroscopy in the presence of Mosher’s acid or by chiral HPLC (see the Supporting Information). [h] Any epimerisation was observed by 1H NMR spectroscopic analysis of the crude reaction mixture. [i] Isolated yields. [j] An inversion of configuration occurred with this electrophile. Such an inversion was verified by NOESY experiments.

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 (cis/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 (−78 °C), the nitrogen inversion is slower with respect to the deprotonation reaction and the kinetic position becomes predominant.[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 2. Temperature-dependent reactivity: lithiation/electrophile-trapping sequence.](image-url)
Table 3. Solvent-dependent reactivity: hydroxyalkylation reactions.

<table>
<thead>
<tr>
<th>Product</th>
<th>R</th>
<th>R'CHO</th>
<th>Yield [%]</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7a-diax</td>
<td>nPr</td>
<td>PhCHO</td>
<td>77</td>
<td>99:1</td>
</tr>
<tr>
<td>7b-diax</td>
<td>nPr</td>
<td>2-furylCHO</td>
<td>59</td>
<td>48:52</td>
</tr>
<tr>
<td>7c-diax</td>
<td>nPr</td>
<td>2,4,6-(CH₃)₃C₆H₂CHO</td>
<td>49</td>
<td>48:52</td>
</tr>
<tr>
<td>7d-diax</td>
<td>nPr</td>
<td>tBuCHO</td>
<td>65</td>
<td>44:56</td>
</tr>
<tr>
<td>7e-diax</td>
<td>Bn</td>
<td>PhCHO</td>
<td>48</td>
<td>47:53</td>
</tr>
<tr>
<td>7f-diax</td>
<td>Bn</td>
<td>2,4,6-(CH₃)₃C₆H₂CHO</td>
<td>45</td>
<td>57:43</td>
</tr>
<tr>
<td>8a</td>
<td>nPr</td>
<td>PhCHO</td>
<td>68</td>
<td>90:10</td>
</tr>
<tr>
<td>8b</td>
<td>nPr</td>
<td>2-furylCHO</td>
<td>77</td>
<td>88:12</td>
</tr>
<tr>
<td>8c</td>
<td>nPr</td>
<td>tBuCHO</td>
<td>62</td>
<td>98:2</td>
</tr>
<tr>
<td>8d</td>
<td>Bn</td>
<td>PhCHO</td>
<td>56</td>
<td>87:13</td>
</tr>
<tr>
<td>8e</td>
<td>nPr</td>
<td>2,4,6-(CH₃)₃C₆H₂CHO</td>
<td>54</td>
<td>2:98</td>
</tr>
<tr>
<td>8f</td>
<td>Bn</td>
<td>2,4,6-(CH₃)₃C₆H₂CHO</td>
<td>49</td>
<td>2:98</td>
</tr>
<tr>
<td>8g</td>
<td>nPr</td>
<td>2-CH₃C₆H₄CHO</td>
<td>69</td>
<td>40:60</td>
</tr>
</tbody>
</table>


The different aggregation state of the lithiated aziridines (i.e., monomeric in THF and dimeric in toluene) 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, diax-7 and 8 were ascertained on the basis of '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 Rₙ,[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 Rₙ showed a more shielded carbonyl methinic proton and a less shielded aziridine methinic proton with respect to the diastereomers with major Rₙ (see the Supporting Information). On the basis of this evidence, the (S,S,S) configuration was similarly assigned also to 7b,e and 7f,e. Consequently, compounds diax-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, diax-8e and diax-8f assigned the (S,R,R) and (S,R,S) absolute configurations to 8a,d and diax-8e,f respectively.[20] A careful inspection of the 'H NMR spectra revealed for the almost single isomer of diax-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 carbionic carbon as responsible for this phenomenon. The presence of broad signals was also verified by 'H NMR spectroscopic analysis of the crude reaction mixtures for the minor isomer of derivatives 8h (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 diax-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 stereochemistry of the addend reaction.

Being unable to obtain suitable crystals, we decided to assign the stereochemistry of 8g and diax-8g by comparison of their 'H NMR spectra with that of compounds 8a and diax-8e with known stereochemistry. Such a comparative 'H NMR spectroscopic analysis was performed in [D₆]toluene at different temperatures (298 and 348 K) on derivatives 8a (as a 90:10 mixture of two diastereomers), diax-8e, 8g and diax-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 (diaz-8a) gave broad signals under the same conditions. In contrast, the 'H NMR spectra of diax-8e and diax-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 '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 diax-8e and diax-8g. In fact, the aziridinyl protons Hₕ (≈ δ = 3.10 ppm) in both 8a and 8g are more shielded with respect to Hₕ (≈ δ = 3.55 ppm) of diax-8e and diax-8g; in addition, methylene protons H₂/H₃ in both 8a and 8g showed similar chemical shifts, and a large ΔΔ (≈ δ = 0.7 ppm) as well as similar chemical shifts were found for Hₕ/Hₕ of diax-8e and diax-8g that were associated with a smaller Δ (≈ δ = 0.35 ppm). All this evidence prompted us to assign the (S,R,R) configuration to 8g and the (S,R,S) configuration to diax-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,[23] and the empirical model proposed by Bassindale and Taylor et al. for the reaction of chiral anions with carbonyl compounds.[24] In this
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. 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.

The reactions of lithiated aziridines cis-1a-Li and trans-1a-Li with ketones were also explored but, unfortunately,
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 8i,j were always obtained with variable amounts of protonated aziridines (cis-1a and trans-1a in toluene) as the result of an acid–base reaction (Scheme 5). This hypothesis was confirmed by treating cis-

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.

For sake of comparison, the usefulness of hydroxyalkylated aziridines 3a-e and 4a-d 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]

Table 4. Temperature-dependent reactivity: hydroxyalkylation reactions.

<table>
<thead>
<tr>
<th>Product[a]</th>
<th>R’R’CO</th>
<th>t [h]</th>
<th>Yield [%][b]</th>
<th>d.r.[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a</td>
<td>(CH₂)₂CO</td>
<td>3.5</td>
<td>82</td>
<td>–</td>
</tr>
<tr>
<td>9b</td>
<td>(CH₂)₂CO</td>
<td>3.5</td>
<td>84</td>
<td>–</td>
</tr>
<tr>
<td>9c diast</td>
<td>p-C₆H₄CHO</td>
<td>3.5</td>
<td>50:50</td>
<td></td>
</tr>
<tr>
<td>10a</td>
<td>(CH₂)₂CO</td>
<td>4</td>
<td>54</td>
<td>–</td>
</tr>
<tr>
<td>10b</td>
<td>PhCO</td>
<td>4</td>
<td>50</td>
<td>–</td>
</tr>
<tr>
<td>10c diast</td>
<td>p-C₆H₄CHO</td>
<td>4</td>
<td>51</td>
<td>50:50</td>
</tr>
</tbody>
</table>

[a] Enantiomeric ratios evaluated by H/NMR spectroscopy in the presence of Mosher’s acid or by chiral HPLC (see the Supporting Information). [b] Isolated yields. [c] Evaluated by 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).


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...
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 aziridinylolithiums cis-1a,b-Li are present, whereas a retentive pathway is observed in toluene, which can likely be ascribed to dimeric trans-configured aziridinylolithiums 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 substitutiation 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 aziridinylolithium (1c-α-Li) has been generated at relatively high temperature (0°C),

![Scheme 7. Reductive ring opening of aziridines: synthesis of chiral 1,2-aminoalcohols.](image1)

![Scheme 8. Synthesis of chiral 1,5-aminoalcohols and phthalans and crystal structure of 14c·HCl.](image2)
thus paving the way for new applications of such reactive inter-
mediates in organometallic chemistry.

Experimental Section

General: THF was freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketile. Petroleum ether refers to the 40–60°C boil-
ing fraction. For the 1H and 13C NMR spectra (1H NMR: 400 MHz, 13C NMR: 150, 100 MHz), CDCl3, CD3OD and [D6]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 17.0% (w/v) aqueous 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/teptic cap technique. Litiathion/ electrophile trapping sequences were performed using a methanol/liquid N2 (−84°C) or acetone/dry ice (−78°C) bath. The enantiomeric ratios were determined by HPLC analysis using a Dacel Chiralcel OD-H column (250 mm x 4.6 mm) or a Cellulose Lux 2 column (250 x 4.6 mm), and by 1H NMR spectroscopy in the presence of Mosher’s acid (1.5 equiv in CDCl3).

General procedure for the ligitation-trapping sequence of aziridines (SS)-1a,b in THF: BuLi (1.5 mmol for 1a and 2 mmol for 1b, 1.4M cyclohexane solution) was added dropwise to a solution of aziridine (SS)-1a or (SS)-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 N2 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 ofaq. NH4Cl (3 mL). The resulting mixture was poured in water (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (Na2SO4) and the solvent evaporated in vacuo. The crude purified by flash chromatography on silica gel (EtOAc/petroleum ether).

(2S,3S)-1-Benzyl-2-ethyl-2,3-diphenylaziridine (3b): Flash chromatography (petroleum ether/EtOAc 95:5), yellow solid, 91%. M.p. 77.8–79.2°C; [α]D20 = +45 (c = 1 in CHCl3); 1H NMR (400 MHz, CDCl3, 298 K): δ = 7.51–7.53 (m, 2H; ArH), 7.30–7.36 (m, 2H; ArH), 7.21–7.25 (m, 1H; ArH), 6.96–7.71 (m, 10H; ArH), 4.27 (d, J=14.1 Hz, 1H; NCH2), 3.94 (d, J=14.1 Hz, 1H; NCH2), 2.86 (s, 1H; NCH), 2.23–3.55 (m, 2H; CH2), 1.93–2.02 (m, 1H; CH); 13C NMR (100 MHz, CDCl3, 298 K): δ = 140.3, 139.5, 138.2, 129.3, 128.2, 128.0, 127.3, 127.6, 126.0, 126.5, 56.3, 56.1, 53.5, 25.9, 11.33 ppm; IR (KBr): ν = 698, 733, 754, 1028, 1073, 1125, 1356, 1452, 1450, 1602, 2875, 2965, 3027, 3060 cm−1; MS (70 eV): m/z (%): 313 (4) [M]+, 312 (3) [M]+; elemental analysis calc'd for C33H36N: C 38.1, H 6.0; found: C 38.2, H 6.3.

1H, 7.1 Hz, 2H; ArH), 7.17–7.34 (m, 6H; ArH), 6.87–6.97 (m, ArH), 6.40 (d, J=6.4 Hz, 2H; ArH), 4.42 (s, 1H; CH2OH), 3.15 (s, 1H; NCH), 2.86–3.00 (m, 1H; CH3CH2), 1.30–1.80 (m, 2H; CH2CH3); 13C NMR (100 MHz, CDCl3, 298 K): δ = 139.9, 137.4, 134.4, 131.7, 128.2, 127.9, 127.5, 127.3, 127.2, 127.1, 126.6, 75.4, 59.8, 57.9, 53.5, 23.3, 12.0 ppm; IR (KBr): ν = 700, 714, 766, 1043, 1450, 1602, 2836, 2861, 2926, 2955, 3057, 3481 cm−1; ESI-MS: m/z: (%): 344 (100) [M]+; elemental analysis calc'd for C6H14NO: C 83.93, N 4.08, H 7.34; found: C 83.66, N 4.07, H 7.30; enantiomeric purity (c.: >98.2) ascertained by 1H NMR spectroscopy in the presence of Mosher’s acid (see the Supporting Information).

(1R,2R,3S,)-2-(Diphenyl-1-propylaziridin-2-yl)phenylmethanol (8a): Flash chromatography (petroleum ether/EtOAc 90:10), white solid, 68%, M.p. 89.8–90.2°C; [α]D20 = +42 (c = 1 in CHCl3); 1H NMR (400 MHz, CDCl3, 298 K): δ = 7.40–7.59 (m, 5H; ArH), 6.86–7.04 (m, 5H; ArH), 1.05 ppm (t, J=7.4 Hz, 3H; CH3); 13C NMR (100 MHz, CDCl3, 298 K): δ = 142.4, 137.5, 134.5, 131.7, 128.2, 127.5, 127.4, 126.9, 126.91, 126.6, 74.3, 58.9, 55.5, 52.8, 24.0, 12.4 ppm; IR (KBr): ν = 698, 760, 784, 846, 915, 940, 1008, 1047, 1076, 1200, 1250, 1455, 1495, 1603, 2869, 2932, 2962, 3029, 3056, 3429 cm−1; ESI-MS: m/z: (%): 344 (100) [M]+, 180 (24); elemental analysis calc'd (c.) for C32H34O: C 83.95, N 4.08, H 7.34; found: C 83.73, N 4.21, H 7.31; enantiomeric purity (c.: >98.2) ascertained by 1H NMR spectroscopy in the presence of Mosher’s acid (see the Supporting Information).
Enantiomeric purity (e.e. > 98.2) ascertained by 1H NMR spectroscopy in the presence of Mosher’s acid (see the Supporting Information).

General procedure for the lithiation–trapping sequence of aziridines (5S)-1 at 0°C: 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 Et2O (10 mL) at 0 °C under an N2 atmosphere. The resulting mixture was stirred for 3.5 h before adding the electrophile (neat if liquid or diluted in 2 mL of Et2O if solid). Then a solution of sat. aq. NH4Cl (3 mL) was added and the mixture poured into water (20 mL) and extracted with Et2O (3 x 10 mL). The combined organic layers were dried (Na2SO4) and the solvent evaporated in vacuo. The crude was purified by flash chromatography on silica gel (EtOAc/petroleum ether).

(2R,3S)-1,3-Dimethyl-2-trimethylsilylphenylaziridine (5e): Flash chromatography (petroleum ether/EtOAc 50:1) gave a solid 35%. M.p. 184.0-185.0°C; [α]D20 +23 (c 1.9 in CHCl3); 1H NMR (400 MHz, CDCl3, 298 K): δ = 7.17–7.21 (m, 2H; ArH); 7.06–7.11 (m, 3H; ArH); 2.74 (s, 3H; NCH3); 1.88 (q, (J(H,H))=5.6 Hz, 1H; CHCH3); 0.92 (d, (J(H,H))=5.6 Hz, 3H; CH3OH); 0.305 ppm (%): MS (70 eV); m/z (%): 219 (24 [M]+), 218 (100) [M]+; 204 (14), 135 (18), 105 (27), 37 (31).

EnantiomERIC purity determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/PrOH 99:1, flow rate 0.4 mL/min. λ = 220 nm; for racemic aziridine, tR = 10.58 min; for enantiomerically enriched, tR = 10.49 min).

(1R,2S,3S)-4-Chlorophenyl-(1,3-dimethyl-2-phenylaziridin-2-yl)methanol (9c): Flash chromatography (petroleum ether/EtOAc 90:20) gave a solid 35%. M.p. 113.0-114.0°C; [α]D20 +22 (+0.9 in CHCl3); 1H NMR (600 MHz, CDCl3, 298 K): δ = 7.32–7.33 (m, 3H; ArH); 7.14–7.15 (4H; ArH); 7.01 (d, (J(H,H))=8.3 Hz, 2H; ArH); 5.07 (s, 1H; CHOH); 2.13 (s, 3H; NCH3), 2.00 (q, (J(H,H))=6.0 Hz, 1H; CHCH3); 1.35 (d, (J(H,H))=6.0 Hz, 3H; CHCH3); 13C NMR (100 MHz, CDCl3, 298 K): δ = 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): v = 704, 730, 820, 1014, 1075, 1090, 1131, 1405, 1449, 1460, 1470, 1500, 1594, 1596, 1620 ppm; 2H); 1H minor; NCH3), 1.67 (s, 3H; minor; NCH3), 1.31 (d, (J(H,H))=4.4 Hz, 3H; CHCH3), 1.20 ppm (d, (J(H,H))=6.0 Hz, 3H; major; CHCH3). 13C NMR (spectra description not provided).

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(1R,2S,3S)-1,3-Dimethyl-2-trimethylsilylphenylaziridine (6c): Flash chromatography (petroleum ether/EtOAc 95:5), colourless oil, 88% as inseparable mixture of isomers (d.r.) 83:17, CDCl3, 263 K). [α]D20 +2.70 (+1.2 in CHCl3); 1H NMR (400 MHz, CDCl3, 298 K): δ = 7.14 (d, (J(H,H))=7.0 Hz, 1H, major; ArH), 7.46 (d, (J(H,H))=7.2 Hz, 1H, major; ArH), 7.29–7.35 (m, 1H major + 2 H minor; ArH), 7.17–7.21 (2H, major; ArH), 7.14 (d, (J(H,H))=7.0 Hz, 1H, minor; ArCH), 2.96 (d, (J(H,H))=2.9 Hz, 1H, minor; ArCHN), 2.56 (s, 3H, major; NCH3), 2.28 (d, (J(H,H))=2.8 Hz, 1H, major; ArCHN), 2.17–2.21 (1H, minor; NHCH3), 1.96–2.06 (3H, 1H, major; NCH3), 2.01 (s, 3H, NCH3); 2H); 139 (d, (J(H,H))=5.0 Hz, CDCl3, 298 K); δ = 143.3, 142.3, 140.9, 138.3, 137.5, 132.5, 130.0, 129.4, 129.7, 128.7, 128.2, 127.6, 127.92, 127.8, 127.1, 122.3, 121.3, 84.4, 84.2, 57.8, 57.8, 48.6, 39.9, 36.7, 29.7, 14.6, 10.9 ppm; IR (film): v = 759, 1013, 1032, 1088, 1171, 1263, 1377, 1402, 1457, 1488, 1601, 2850, 2920, 2957, 3413 ppm; ESIMS; m/z (%): 288 (100) [M]+. 4-

(1S,2S,3S)-4-Chlorophenyl-(1,3-dimethyl-2-phenylaziridin-2-yl)methanol (10c): Flash chromatography (petroleum ether/EtOAc 20:80), white solid. 28% as inseparable mixture of isomers (d.r.) = 87:13, CDCl3, 298 K). [α]D20 +4.99 (+2.2 in CH2Cl2); 1H NMR (400 MHz, CDCl3, 298 K): δ = 7.00–7.19 (m, 8H; major; ArH), 6.87–6.89 (m, 1H, minor; ArH), 6.17 (s, 1H, minor; CHOCH3), 5.60 (s, 1H, major; CHOH), 3.28 (d, (J(H,H))=4.0 Hz, 1H, minor; ArCHN), 2.04 (d, (J(H,H))=3.3 Hz, 1H, major; ArCH), 1.94–2.00 (m, 1H major + 4H minor; NCH2), 1.90 (s, 3H, minor; NCH3), 1.67 (s, 3H, minor; NCH3), 1.31 (d, (J(H,H))=4.4 Hz, 3H, minor; CHCH3), 1.20 ppm (d, (J(H,H))=6.0 Hz, 3H, major; CHCH3). 13C NMR (spectra description not provided).
2H; ArH), 2.97 (s, 2H; ArCH), 2.30–2.41 (m, 2H; NCH), 1.66–1.81 (m, 2H; CH2), 1.40–1.49 (m, 2H; CH2), 0.89 (t (J(1,2H) = 7.4 Hz, 3H; CH3), 0.83 ppm (t (J(1,2H) = 7.3 Hz, 3H; CH3)); 13C NMR (150 MHz, CDCl3, 298 K): δ = 145.5, 145.7, 137.0, 130.3, 127.7, 126.1, 126.0, 125.95, 61.8, 43.9, 43.7, 28.5, 23.8, 12.0, 7.8 ppm; IR (film): δ = 703, 751, 765, 1039, 1075, 1151, 1379, 1456, 1599, 2872, 2927, 2962, 3024, 3052, 3080, 3336 cm⁻¹; ESI-MS: m/z (%): 268 (100) [M-H]⁻; elemental analysis calc (%) for C29H30N+O6: C 74.61, H 6.16; found: C 75.41, H 6.87. Enantioemic purity determined by HPLC analysis (Cellulose-2, hexane/PrOH 99.5:0.5, flow rate 0.6 mL/min, λ = 260 nm; for racemic amine, t1 = 5.75 min, t2 = 6.00 min; for enantiomerically pure amine, t1 = 5.75 min).

(S)-1,2-Diphenyl-1-(propylamino)-2-amine (en)-11a): Colourless oil, 55%. 

4,21 (s, 3H; NCH3), 3.65 ppm (d, (J(1,3H) = 6.6 Hz, 3H; CH2)); 13C NMR (100 MHz, CDCl3, 298 K): δ = 134.2, 134.3, 130.4, 128.4, 127.2, 126.7, 125.5, 74.0, 58.6, 55.1, 30.0, 13.7 ppm; IR (KBr): δ = 704, 703, 1057, 1453, 1602, 2851, 2932, 3024, 3350 cm⁻¹; ESI-MS: m/z (%): 256 (100) [M-H]⁻; elemental analysis calc (%) for C29H30N+O6: C 74.61, H 6.16; found: C 75.41, H 6.87. Enantioemic purity determined by HPLC analysis (Daicel Chiralcel OD-H column, hexane/PrOH 95:5, flow rate 0.8 mL/min, λ = 210 nm; for racemic amino alcohol, t1 = 15.67 min, t2 = 19.41 min; for enantiomerically enriched amino alcohol, t1 = 19.70 min).

(S)-2-[2-(methylthio)phenyl]diphenylmethanol (15): Flash chromatography with CH2Cl2 (1:2) as eluent. 75% yield.

Acknowledgements

This work was carried out under the framework of the national project “Stereoeselecitve in Sintesi Organica. Metodologie ed Applicazioni” and financially supported by the University of Bari and by the Interuniversities Consortium C.N.I.M.P.I.S. The authors would like to acknowledge Professor Varinder Aggarwal of the University of Bristol for providing some high-resolution mass analyses, and Giuseppe Chita and Caterina Mansueto of the Istituto di Cristallografia of CNR in Bari for their technical assistance.


[11] The structure and configuration of cis-1-a-Li and trans-1-a-Li have been ascertained by a multinuclear magnetic resonance investiga-
These assignments seem to be the better choice in terms of fitting with the observed stereochemistry.

[25] It cannot be ruled out that a differnt 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 also been 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.


[28] The lower yields that were observed when starting from trans-azidines 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.


Received: July 29, 2010
Published online: November 12, 2010