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α- vs Ortho-Lithiation of *N*-Alkylarylaziridines: Probing the Role of the Nitrogen Inversion Process†

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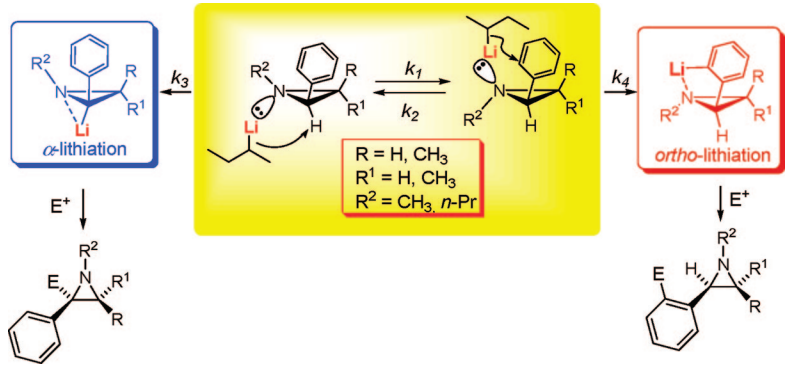

The lithiation reaction of monophenyl- and diphenylaziridines has been investigated in detail in an effort to understand why the former undergo exclusively or mainly ortho-lithiation while the latter are lithiated exclusively at the α-position. Evidence is reported that ruled out the possibility that the α-lithiation, observed for the diphenylaziridines, is the result of an ortho- to α-translocation phenomenon, thus substantiating a direct α-deprotonation process. The role of the aziridine nitrogen lone-pair has been considered: dynamics at the aziridine nitrogen as well as complex-induced proximity effects seem to be responsible for the observed regioselectivity in both monophenyl and diphenylaziridines. It turns out that, by tuning the reaction conditions for the lithiation of *trans*-1-alkyl-2-methyl-3-phenylaziridines, it is possible to generate with high regioselectivity α- and/or ortho-lithiated aziridines, which can be stereoselectively functionalized by electrophilic trapping. A regioselective ortho-functionalization of diphenylaziridines is made possible by halogen− or tin−lithium exchange and by deprotonation of bis-deuterated aziridines.

Introduction

Lithiation of simpler and easily available aziridines followed by trapping with electrophiles is undoubtedly an appealing methodology for making more functionalized aziridines, which are useful building blocks in stereoselective synthesis.[1,2] The regioselectivity of the lithiation step substantially depends upon the nature of the aziridine ring substituents[3] as well as on the stereochemistry at the nitrogen atom (related to the rate of inversion). Indeed, while with an electron-withdrawing group [i.e., R(Ar)SO_2, Boc] as the *N*-substituent deprotonation at the aziridine carbon atoms is always observed,[4] a more complex situation results, instead, when the nitrogen substituent is an electron-releasing group (i.e., alkyl, benzyl).[5]

† Dedicated to Prof. Peter Beak of the Department of Chemistry of the University of Illinois at Urbana−Champaign.

(1) (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325. (b) Hodgson, D. M.; Bray, C. D.; Humphreys, P. G. *Synlett* **2006**, 1–22. For a special issue on oxiranyl and aziridinyl anions (Florio, S., Ed.), see: (c) Florio, S. *Tetrahedron* **2003**, *59*, 9693. (d) Hodgson, D. M.; Bray, C. D. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006, p 145.

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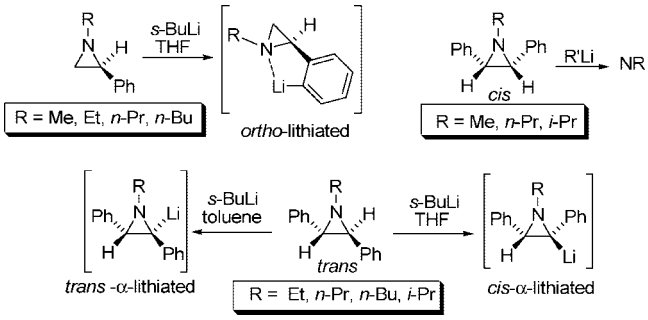
SCHEME 1



Thus, while 1-alkyl-2-arylaziridines are smoothly ortho-lithiated, surprisingly *trans*-1-alkyl-2,3-diphenylaziridines are regioselectively α-lithiated with a stereochemistry that is controlled by the reaction medium (i.e., inversion in THF and retention in toluene). Yet, unexpectedly, *cis*-1-alkyl-2,3-diphenylaziridines are not lithiated at all (Scheme 1).[6]

Additionally, further studies in this context (a detailed multinuclear magnetic resonance investigation) proved that lithiated species derived from *trans*-1-alkyl-2,3-diphenylaziridines are cis configured in THF and trans in toluene.[7]

Having proved the synthetic utility and ascertained the structural features of such lithiated aziridines, we became successively concerned with the lithiation mechanism and the α- vs ortho competition observed in the lithiation of monophenyl- and *trans*-diphenylaziridines. The results of this investigation are reported herein.

Results and Discussion

In principle, there are two possibilities that could be envisaged in the α-lithiation of the *trans*-2,3-diphenylaziridines *trans*-**1** (Scheme 2), (a) direct α-deprotonation and (b) ortho-lithiation, giving **2-Li**, followed by an ortho/α-translocation (a kinetically favored ortho deprotonation and subsequent thermodynamically more acidic benzylic proton removal). The latter possibility has to be taken into consideration because the four-center transition state TS-**A** (assumable exclusively for **2-Li**) would explain the different regioselectivity observed in the lithiation of the *N*-alkyl-2-phenylaziridines, where, due to the presence of only one benzylic hydrogen, exclusive ortho-lithiation takes place.

In order to get more insight on the lithiation mechanism of arylaziridines, some solving experiments were conducted on

SCHEME 2

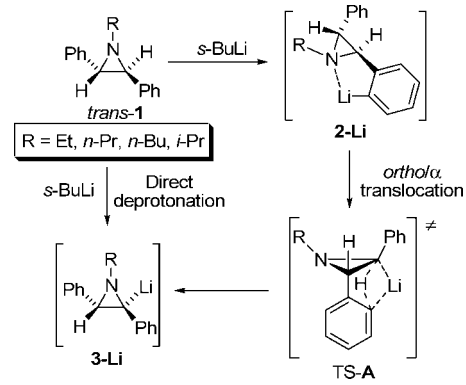
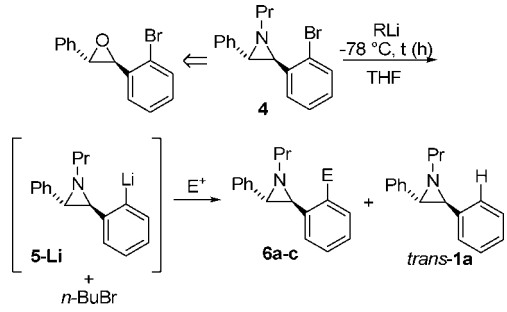


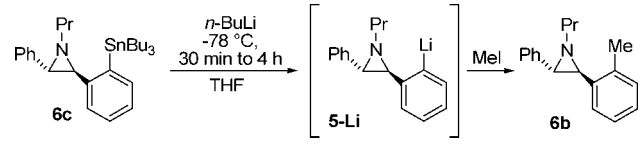
TABLE 1. Lithium−Bromine Exchange of Aziridine 4



entry	*t*	RLi	E	aziridine **6** (% yield)[a]	ratio **6**/*trans*-**1a**[b]
1	1 h	*n*-BuLi	D	**6a** (53)	53/47
2	1 h	*n*-BuLi	Me	**6b** (70)	80/20
3	4 h	*n*-BuLi	Me	**6b** (50)	45/55
4	1 h	*t*-BuLi	Me	**6b** (60)	60/40
5	4 h	*t*-BuLi	Me	**6b** (0)	1/99
6	20 min	*n*-BuLi	Bu_3Sn	**6c** (56)[c]	−[d]

[a] Estimated by ^{1}H NMR and GC−MS analysis. [b] From ^{1}H NMR of the crude. [c] Isolated yield. [d] By GC−MS analysis less than 10% of *trans*-**1a** can be estimated.

SCHEME 3



alternatively generated ortho-lithiated aziridines and on deuterium-labeled aziridines.

In the first of these experiments, the *o*-bromoaziridine **4**, prepared from *o*-bromostilbene oxide,[8] was subjected to lithium/bromine exchange with organolithiums (*n*-BuLi, *t*-BuLi) to give the ortho-lithiated aziridine **5-Li** (Table 1), which furnished, upon deuteration or methylation, ortho-substituted products **6a,b** and aziridine *trans*-**1a**, which likely originates from the deprotonation, by **5-Li**, of the resulting alkyl bromide (*n*-BuBr or *t*-BuBr) formed in the reaction medium in the Li−Br exchange. In order to optimize this reaction, several conditions were verified (Table 1).

All the attempts to quantitatively generate **5-Li** and capture it by deuteration or methylation using the standard time of the

(2) (a) Lowden, P. A. S. In *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2006, p 399. (b) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080–2135. (c) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247–258. (d) McCoull, W. M.; Davis, F. A. *Synthesis* **2000**, *134*, 7–1365. (e) Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599–619.

(3) Because of the electronic effect of the *N*-substituent on the reactivity of the aziridines, it could be useful to classify as activated those aziridines bearing an electron-withdrawing group and as nonactivated the ones with an electron-releasing group as the nitrogen substituent.

(4) (a) Luisi, R.; Capriati, V.; Florio, S.; Ranaldo, R. *Tetrahedron Lett.* **2003**, *44*, 2677–2681. (b) Luisi, R.; Capriati, V.; Florio, S.; Di Cunto, P.; Musio, B. *Tetrahedron* **2005**, *61*, 3251–3260. (c) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153–1156. (d) Hodgson, D. M.; Miles, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 949–952. (e) O'Brien, P.; Rosser, C. M.; Caine, D. *Tetrahedron* **2003**, *59*, 9779–9791. (f) Breternitz, H. J.; Schaumann, E.; Adiwidjaja, G. *Tetrahedron Lett.* **1991**, *32*, 1299–1302.

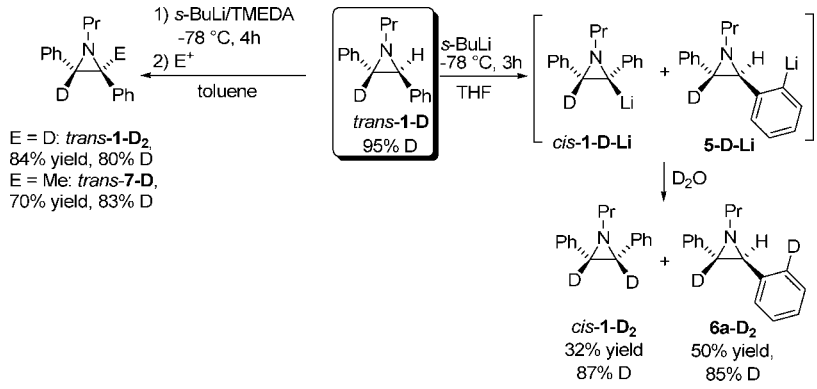
(5) (a) Luisi, R.; Capriati, V.; Di Cunto, P.; Florio, S.; Mansueto, R. *Org. Lett.* **2005**, *9*, 3925–3928. (b) Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005**, *7*, 3749–3752.

(6) Luisi, R.; Capriati, V.; Florio, S.; Musio, B. *Org. Lett.* **2007**, *9*, 1263–1266.

(7) Capriati, V.; Florio, S.; Luisi, R.; Mazzanti, A.; Musio, B. *J. Org. Chem.* **2008**, *73*, 3197–3204.

(8) (a) Akguen, E.; Glinski, M. B.; Dhawan, K. L.; Durst, T. *J. Org. Chem.* **1981**, *46*, 2730–2734. (b) Anderson, W. K.; Milowsky, A. S. *J. Med. Chem.* **1986**, *29*, 2241–2249.

SCHEME 4



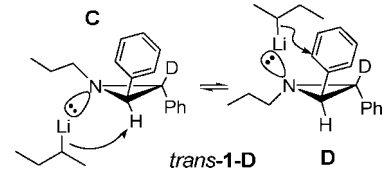
deprotonation reaction (3−4 h) failed, giving mainly *trans*-**1a**. The intermediate **5-Li** could be efficiently trapped with electrophiles only within 1 h (Table 1, entries 1, 2, 4) or less (entry 6). In any case, under the above conditions, no trace of the α-functionalized derivatives was observed, suggesting that no translocation occurs. In the second experiment, the aziridine **6c** was subjected to the tin−lithium exchange reaction in order to avoid the formation of *trans*-**1a** (Scheme 3). The resulting ortho-lithiated aziridine **5-Li** was kept at low temperature up to 4 h and then quenched with MeI to furnish exclusively the ortho-methylated aziridine **6b** (57% isolated yield), once more suggesting that no translocation had taken place.

Other experiments were executed on deuterated aziridine *trans*-**1-D** (Scheme 4), which was subjected to lithiation in THF[9] under standard conditions (*s*-BuLi, −78 °C, 4 h), giving bis-deuterated compounds *cis*-**1-D$_2$** (32% isolated yield) and **6a-D$_2$** (50% isolated yield) upon quenching with D_2O (ratio α/ortho 55:45 from ^{1}H NMR of the crude). Compound *cis*-**1-D$_2$** likely originates from *cis*-**1-D-Li** (the expected lithiated species in THF), while **6a-D$_2$**, unexpectedly for diphenylaziridines, should derive from ortho-lithiated intermediate **5-D-Li**.[10] By contrast, deprotonation of *trans*-**1-D** in toluene furnished, upon quenching with D_2O or MeI, α-functionalized aziridines *trans*-**1-D$_2$** and aziridine *trans*-**7-D** with complete retention of configuration.

It must be pointed out that, in all the reactions in Scheme 4, there is some deuterium erosion with respect to the starting material, testifying that a kinetic isotope effect is operative and a competitive α-dedeuteration occurs.[11]

To explain the formation of **5-D-Li** in THF, the role of the aziridine ring nitrogen and complexation phenomena must be considered.[12] It has been proved that aziridines like *trans*-**1-D** exist as an equilibrating mixture of the two invertomers **C** and **D** (Scheme 5) in a 50:50 ratio.[6] Therefore, with the assumption that a precomplexation to the base is a prerequisite for the deprotonation to occur and that a kinetic isotope effect is operative,[13] the deprotonation should take place at the more

SCHEME 5



easily removable protons for proximity reasons, namely, the ortho position for the invertomer **D** and the α-position for **C**.[14] Accordingly, α-lithiation of **C**, occurring after the complex formation between *s*-BuLi and starting aziridine, followed by trans to cis isomerization (in THF), would generate *cis*-**1-D-Li** and then, after trapping with D_2O, *cis*-**1-D$_2$**. On the other hand, invertomer **D** would undergo either ortho-deprotonation or α-dedeuteration, the ortho-deprotonation being preferred likely because of a kinetic isotope effect.[15]

The different result obtained in toluene, that is, exclusive α-lithiation, could be tentatively ascribed to the different aggregation state of the lithiating agent[16] and/or to a more marked difference in kinetic and thermodynamic acidity between the protons to be removed in this solvent.

To definitely prove that no translocation occurs, aziridine *trans*-**1-D$_2$** was subjected to deprotonation in THF under standard conditions (Scheme 6).

Upon quenching with MeI, α-methylated aziridine *cis*-**7-D** and ortho-methylated aziridine **6b-D$_2$** were the only products identified in the ^{1}H NMR of the crude products in a 20:80 ratio, respectively. This outcome clearly demonstrates that no translocation occurs because the expected α-methylated aziridine *cis*-**7-D$_2$** that would result from the trapping of **8-Li** was not found. Moreover, a comparison of the α/ortho ratios observed in the deprotonation/trapping sequences of *trans*-**1-D** and *trans*-**1-D$_2$**

(9) α-Lithiation in this coordinating solvent would give an isomerized cis aziridine (see ref 7).

(10) On the basis of the model depicted in Scheme 5, we assume that the phenyl group linked to the CH of the aziridine ring is ortho-lithiated, because of a concomitance of a kinetic isotope effect and a proximity effect. It is worth noting that ortho-lithiation has never been observed with undeuterated aziridines *trans*-**1** (see ref 6).

(11) A value of $k_H/k_D > 5$ can be estimated for the α-deprotonation considering the loss of deuterium in aziridine *cis*-**1-D$_2$** (87% D), *trans*-**7-D** (83% D), and *trans*-**1-D$_2$** (80% D) with respect to the starting aziridine *trans*-**1-D** (95% D).

(12) For examples of assisted deprotonation, see: (a) Bertini Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315–321. (b) Itami, K.; Kamei, T.; Mitsudo, K.; Nokami, T.; Yoshida, J. *J. Org. Chem.* **2001**, *66*, 3970–3976.

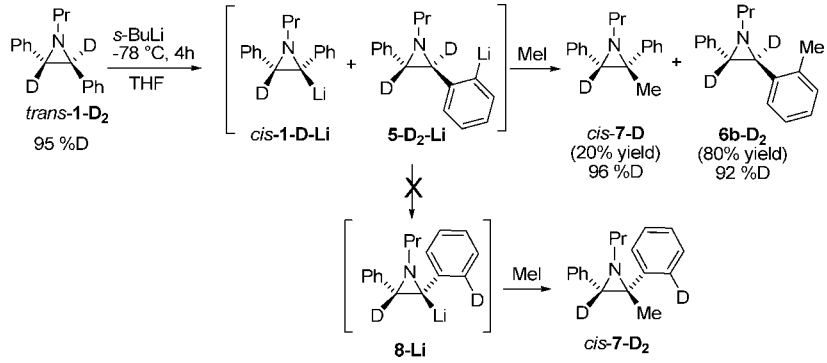
(13) The kinetic isotope effect could suggest if the deprotonation step is rate-determining and a precomplexation could be involved. See related studies: (a) Resek, J. E.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 405–406. (b) Meyers, A. I.; Dickman, D. A. *J. Am. Chem. Soc.* **1987**, *109*, 1263–1265.

(14) This could be an example of complex-induced proximity effect as exhaustively reported: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–2225.

(15) Related mechanistic studies on deuterium-labeled systems have been reported. See: (a) Fernandez, I.; Gonzalez, J.; Lopez-Ortiz, F. *J. Am. Chem. Soc.* **2004**, *126*, 12551–12564. (b) Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* **2004**, *6*, 4191–4194. (c) Clayden, J.; Pink, J. H.; Westlund, N.; Wilson, F. X. *Tetrahedron Lett.* **1998**, *39*, 8377–8380. (d) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561–11570.

(16) (a) Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145–8153. (b) Thomas, R. D.; Jensen, R. M.; Young, T. C. *Organometallics* **1987**, *6*, 565–571. (c) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371–2379. (d) Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984**, *106*, 255–256.

SCHEME 6



(55:45 and 20:80, respectively) clearly show that a kinetic isotope effect is responsible for the increased ortho regioselectivity obtained in the lithiation of *trans*-**1-D$_2$**, accordingly with the model shown in Scheme 5.[13]

The questions that rise at this point are the following: if no ortho/α-translocation process intervenes, why are *N*-alkyl-monophenylaziridines regioselectively ortho-lithiated, whereas *trans*-*N*-alkyl-2,3-diphenylaziridines are regioselectively α-lithiated? If we assume that the ortho-lithiation is a kinetically favored process and that the α-lithiation is the thermodynamic one, because of the higher acidity of the benzylic protons, which factors should be considered to address the regioselectivity?

In order to answer these questions and give an explanation to the experimental results, the deprotonation/trapping sequence of the aziridines *trans*-**9a,b** was investigated under several conditions (Table 2).

Lithiation of *trans*-**9a**, at low temperature and in different solvents (entries 1−6), occurred mainly at the ortho position giving *ortho*-**9a-Li**, which furnished aziridines **11a,b** as the main products upon reaction with electrophiles.[17] Upon raising the temperature to 0 °C, a complete inversion of regioselectivity was observed (entries 7, 8) and the α-functionalized aziridines **10a,b**, resulting from the trapping of α-**9a-Li**, were obtained.[18] In order to verify if, for instance, the observed change in regioselectivity was due to a temperature-induced ortho/α-translocation, *trans*-**9a** was deprotonated in Et_2O at low temperature (−78 °C) and then warmed up to 0 °C before quenching with MeI: the same result as entry 6 was obtained, thus excluding once more the translocation.

Similar results were obtained in the deprotonation/electrophilic trapping sequence of *trans*-**9b**; once more the reactions performed at low temperature (−70 °C)[19] (entries 10−12) led mainly to ortho-functionalized aziridines **11c,d**, likely deriving from the quenching of *ortho*-**9b-Li**. On the contrary, the same sequence conducted at higher temperature (0 °C) furnished, as the main products, α-functionalized aziridines **10c,d**.[17]

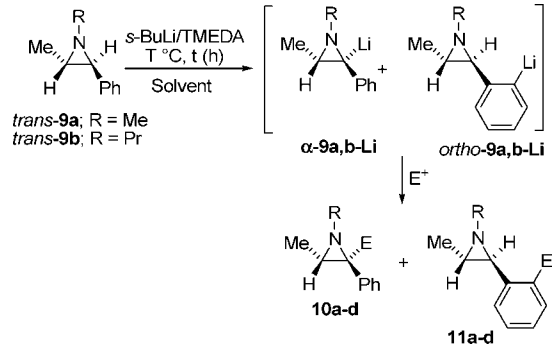
A reduced reactivity with respect to that of the aziridine *trans*-**9a** was observed when the isomer *cis*-**9a** was subjected to deprotonation (*s*-BuLi/TMEDA in THF at −78 °C) followed by trapping with D_2O and MeI. Only 30% of ortho-functionalized products **13a,b** was recovered together with unreacted starting material (Scheme 7).

(17) Compounds **11a−d** and **10a−d** have been isolated and fully characterized (see the Supporting Information).

(18) Under these conditions, an undesired deprotonation of THF and toluene intervenes, making Et_2O the solvent of choice.

(19) The reaction is slower at −78 °C, likely because of a nitrogen substituent effect.

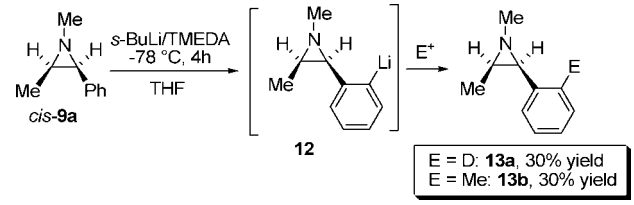
TABLE 2. Lithiation/Electrophile Trapping Sequence of Aziridine *trans*-9a,b



entry	aziridine *trans*-**9**	solvent	*T* (°C)	*t* (h)	E	aziridine **10**	aziridine **11**	ratio **10/11**
1	*trans*-**9a**	THF	−78	4	D	**10a**	**11a**	—[a,b]
2	*trans*-**9a**	THF	−78	4	Me	*cis*-**10b**[e]	**11b**	14/86[c]
3	*trans*-**9a**	toluene	−78	4	D	**10a**	**11a**	—[a,b]
4	*trans*-**9a**	toluene	−78	4	Me	**10b**	**11b**	13/87[c]
5	*trans*-**9a**	Et_2O	−78	4	D	**10a**	**11a**	—[a,b]
6	*trans*-**9a**	Et_2O	−78	4	Me	**10b**	**11b**	10/90[c]
7	*trans*-**9a**	Et_2O	0	3.5	D	**10a**	**11a**	—[a,d]
8	*trans*-**9a**	Et_2O	0	3.5	Me	**10b**	**11b**	97/3[c]
9	*trans*-**9a**	Et_2O	−40	4	Me	**10b**	**11b**	34/66[c]
10	*trans*-**9b**	THF	−70	6	D	**10c**	**11c**	—[a,b]
11	*trans*-**9b**	THF	−70	6	Me	**10d**	**11d**	10/90[c]
12	*trans*-**9b**	Et_2O	−70	6	Me	**10d**	**11d**	20/80[c]
13	*trans*-**9b**	Et_2O	0	4	D	**10c**	**11c**	—[a,d]
14	*trans*-**9b**	Et_2O	0	4	Me	**10d**	**11d**	97/3[c]

[a] Deuterium incorporation > 92%. Aziridines **10a** and **11a** are undistinguishable by ^{1}H NMR analysis. The ortho/α ratio can be estimated from the integral values between the aromatic and benzylic protons. [b] Under these conditions, the main product is the ortho-deuterated derivative. [c] From ^{1}H NMR and GC−MS analyses of the crude. [d] Under these conditions the main product is the α-deuterated derivative. [e] An inversion of configuration occurs in this solvent upon quenching with MeI.

SCHEME 7



This result is not surprising considering that it has been reported that *cis*-*N*-alkyl-2,3-diphenylaziridines are not lithiated at all under the same conditions, likely due to a steric interaction between the cis positioned substituents.[6]

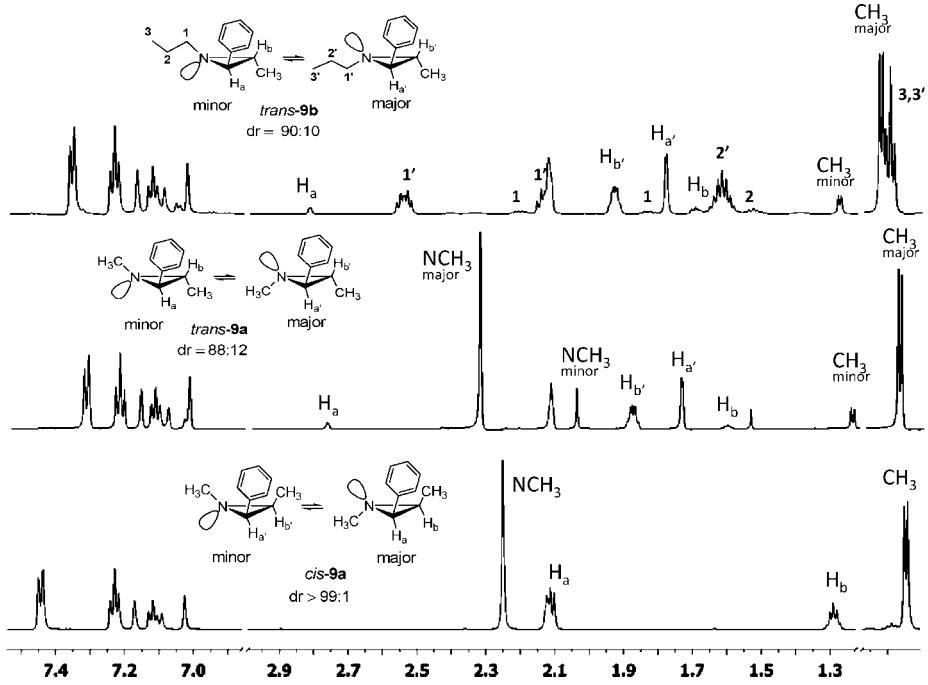


FIGURE 1. Comparison of ^{1}H NMR spectra of aziridines *trans*-**9a,b** and *cis*-**9** in toluene-d_8 at 223 K under slow exchange conditions.

In order to find an explanation for the different reactivity and regioselectivity between aziridines *trans*-**9a,b** and *cis*-**9a**, again the role of the aziridine ring nitrogen configuration should be considered. ^{1}H NMR experiments unequivocally demonstrated that aziridines *trans*-**9a,b** exist, at low temperature, as a mixture of two slowly equilibrating invertomers[20] (dr ≈ 88:12 to 90:10), whereas aziridine *cis*-**9a** shows the signals of one main invertomer (dr > 99:1) under the same conditions (Figure 1).[21]

The nitrogen configuration has been ascertained by selective NOESY experiments under slow exchange conditions for both *trans*-**9a,b** and *cis*-**9a** (Figure 2).[22] In all cases the main invertomers are those that set the lone pairs from the same side of the phenyl ring.

According to the proposed model reported in Scheme 5 and assuming a precomplexation between the base and the aziridine prior to the deprotonation, the regioselectivity can be explained by considering the relative rates of the deprotonation reactions (k_3, k_4) with respect to the rate of nitrogen inversion (k_1, k_2) (Scheme 8).[23]

If we assume that the proximity effect complex **F** in Scheme 8 should give *ortho*-lithiation and complex **E** α-lithiation, we can answer all the questions above. In the lithiation of *trans*-**9a,b** carried out at low temperature, where the rate of nitrogen inversion is low (two invertomers can be detected under the NMR time scale) and likely k_1 and k_2 are much lower than k_4 and k_3, the major invertomer, that is, the one that puts the lone pair on the same side of the phenyl ring, would form complex **F** and then undergo ortho-lithiation. Examining the data in Table 2, at −78 °C, we note an ortho/α ratio ranging from 86:14 to 90:10 in the lithiation trapping sequence of *trans*-**9a** (entries 2, 4, 6), likely reflecting the ratio between the two invertomers, that is, 88:12 in toluene-d_8 and 90:10 in THF-d_8.[24] When the temperature is raised to 0 °C, a complete inversion of regioselectivity is observed (ortho/α ratio 3:97, entry 8) that can be justified with the Curtin−Hammett principle by assuming k_1, $k_2 \gg k_3 > k_4$. Similar conclusion can be drawn for aziridine *trans*-**9b** (entries 11, 12, 14).[25]

In the case of aziridine *cis*-**9a**, the only detectable invertomer, at −78 °C, is the one that puts the lone pair on the same side of the phenyl ring; therefore, the interaction with the lithiating agent would give complex **F** and then ortho-lithiation, as experimentally observed (here again likely k_1, $k_2 \ll k_4$ and k_3). The cis relationship between the methyl group and the phenyl ring could cause steric hindrance and reduce the reactivity. Accordingly, 1-methyl-2-phenylaziridine, existing as the sole invertomer that puts the lone pair on the same side of the phenyl ring, is exclusively ortho-lithiated.

To further support this hypothesis, we decided to perform some more experiments at higher temperature on aziridines *cis*-**9a** and **14**[26] with the idea that an enhancement of the interconversion rate (k_1, k_2) between the two invertomers could promote the thermodynamically favored benzylic deprotonation, which actually proved to be favored at 0 °C in the case of *trans*-**9a,b**.

The lithiation/trapping sequence of aziridines *cis*-**9a** and **14** (Scheme 9) led to a mixture of α-functionalized aziridines **10b**

(20) For some studies on the aziridine nitrogen inversion, see: (a) Johnston, E. R. *Magn. Reson. Chem.* **1995**, *33*, 664–668. (b) Kessler, H. *Angew. Chem., Int. Ed.* **1970**, *9*, 219–235. (c) Jennings, W. B. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992, p 105.

(21) The same diastereomeric ratio was observed at lower temperature and in a different solvent, such as THF-d_8.

(22) Neuhaus, D.; Williamson, M. In *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH: New York, 1989, p 264.

(23) For examples of reactivity in conformationally mobile systems, see: (a) Seeman, J. I.; Secor, H. V.; Hartung, H.; Galzerano, R. *J. Am. Chem. Soc.* **1980**, *102*, 7741–7747. (b) Oki, M. *Acc. Chem. Res.* **1984**, *17*, 154–159. (c) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134.

(24) On the basis of the experimental results, it is likely that a similar invertomer distribution could be also present in Et_2O.

(25) It seems that the nitrogen substituent could affect significantly only the reactivity (longer reaction times) and not the regioselectivity.

(26) It has been already reported that aziridine **14** exists as one main invertomer, analogously to *cis*-**9a**, (dr > 99:1), which puts the lone pair on the same side of the phenyl ring (see ref 5b).

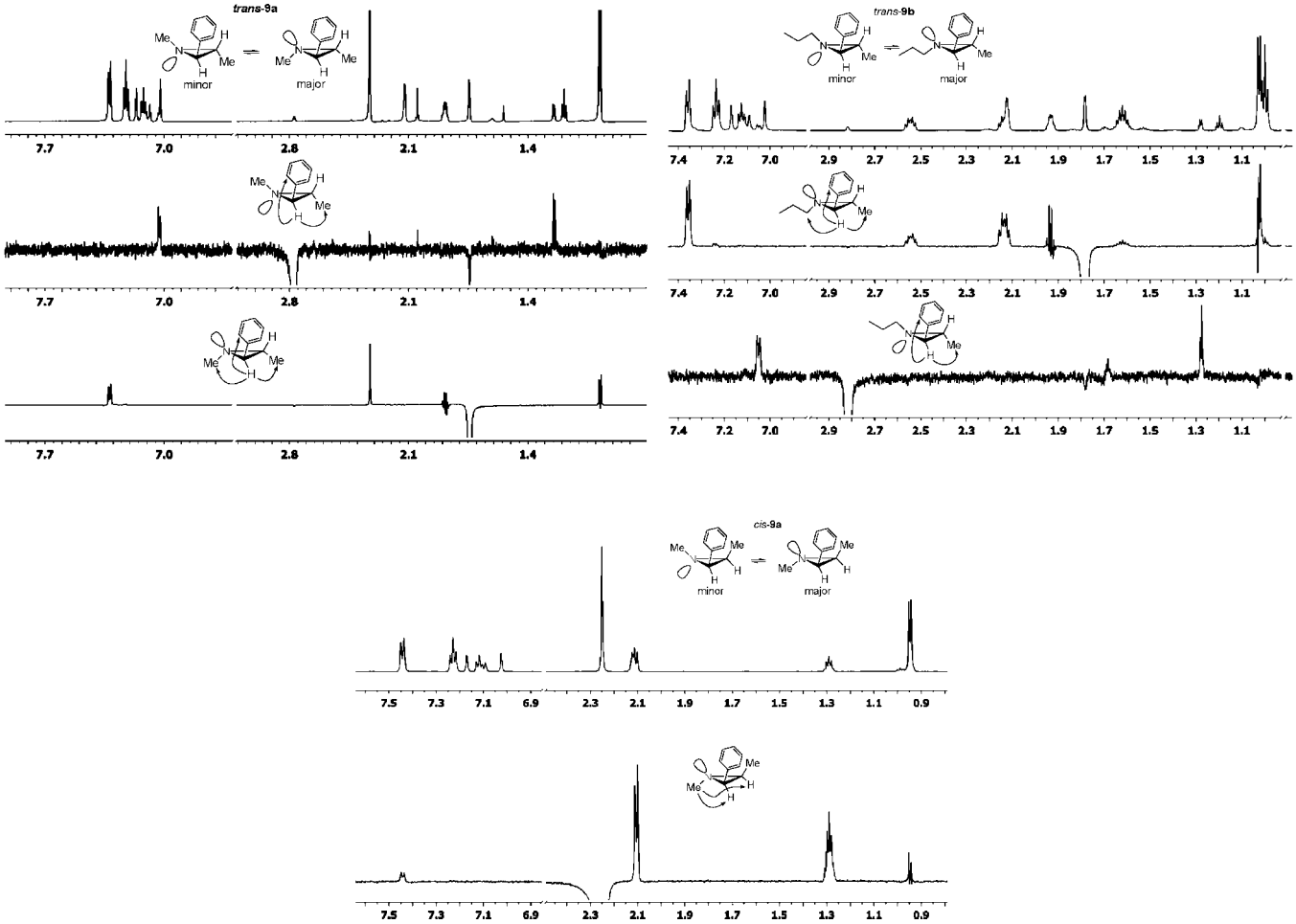
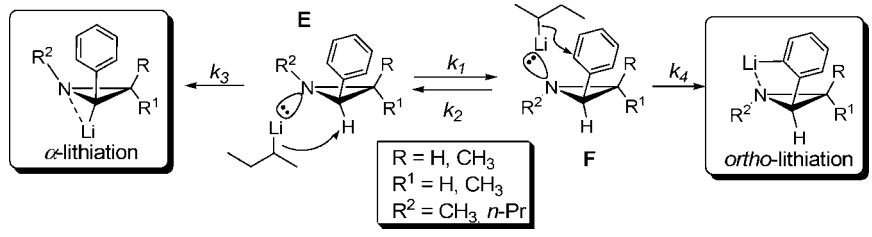


FIGURE 2. NOESY-1D spectra of aziridines *trans*-**9a,b** and *cis*-**9** in toluene-d_8 at 223 K under slow exchange conditions.

SCHEME 8

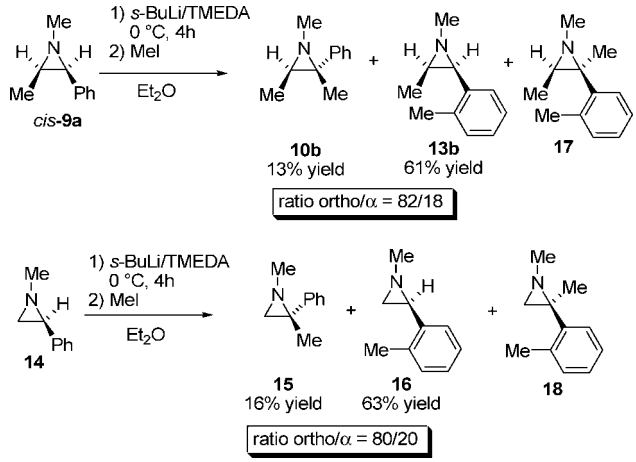


and **15** (13% and 16% yield, respectively) and ortho-functionalized aziridines **13b** and **16** (61% and 63% yield, respectively), and the ortho/α ratio in both cases was around 80/20. Bis-functionalized derivatives **17** and **18** were also detected (24% and 19% yield, respectively), likely derived from a double lithiation.[27]

The presence of α-functionalized aziridines **10b** and **15** in the reaction mixture could be ascribed to α-lithiated intermediates resulting from complexes of the kind **E** (Scheme 8), which are favored under thermodynamic conditions.

From the above results, it seems that the rate of the nitrogen inversion is responsible for the observed regioselectivity; we reasoned that performing the lithiation/trapping sequence of *trans*-**9a** at an intermediate temperature (i.e., −40 °C) where likely k_1, $k_2 \approx k_4$ and k_3, both the ortho- and α-functionalized aziridines should be obtained. An ortho/α ratio of 66/34 was observed (Table 2, entry 9) upon quenching with MeI, proving once more the role of the nitrogen inversion.

SCHEME 9



Conclusion

To summarize, all the above results seem to exclude that the α-lithiation of *trans*-2,3-diphenylaziridine **1** arises from an ortho- to α-translocation phenomenon, while they substantiate the crucial role of the aziridine nitrogen dynamics in controlling the α- vs ortho-lithiation competition. For both the α- and ortho-lithiation a model can be proposed on the basis of a complex-induced proximity effect (CIPE), where the first event is the precomplexation of the lithiating agent at the nitrogen lone-pair and then, if the proximity arrangement is realized, α or ortho or both deprotonations occur. It is remarkable that controlling the rate of the nitrogen inversion could make the lithiation site predictable and also that for the first time an α-lithiated aziridine has been generated at relatively high temperature (0 °C). Finally, the resulting lithiated species react with electrophiles (with or without isomerization in the case of the α-lithiated species) to give the corresponding α- or ortho-substituted aziridines. Further studies are actually underway in order to exploit the above results for planning stereoselective syntheses and unravel the role of the aziridine nitrogen.

(27) Attempts to isolate compounds **17** and **18** failed. They were recognized by GC−MS analysis and by ^{1}H NMR of the crude.

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Supporting Information Available: General procedures, spectral data, and copies of NMR spectra for all the compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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