ORGANIC LETTERS

2007
Vol. 9, No. 7
1263−1266

Regio- and Stereoselective Lithiation and Electrophilic Substitution Reactions of *N*-Alkyl-2,3-diphenylaziridines: Solvent Effect†

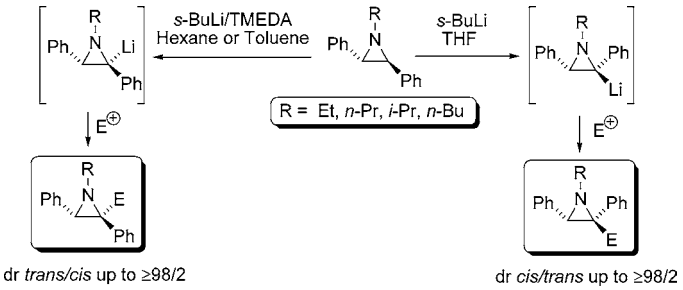
Renzo Luisi, Vito Capriati, Saverio Florio,* and Biagia Musio

Dipartimento Farmaco-Chimico, Università di Bari, C.N.R; Istituto di Chimica dei Composti OrganoMetallici "ICCOM", Sezione di Bari, Via E.Orabona 4, I-70125 Bari, Italy

florio@farmchim.uniba.it

Received January 10, 2007

ABSTRACT



The lithiation reaction of *cis*- and *trans*-*N*-alkyl-2,3-diphenylaziridines has been investigated. While *cis*-diphenylaziridines do not undergo any lithiation upon treatment with organolithiums, the lithiation reaction of the *trans* counterparts is completely α-regioselective and the stereochemical course of the lithiation-trapping sequence is solvent dependent: inversion of configuration in coordinating solvents (THF or toluene/crown ether) and retention in hexane, ether, or toluene. The preparation of stereodefined functionalized *N*-alkyl-2,3-diphenylaziridines is described.

The "aziridinyl anion methodology" (AAM), based on the metalation-trapping sequence of an easily available parent aziridine, has become an attractive way of making functionalized aziridines.[1,2] Most studies in this area have focused on systems where the anion bearing carbon atom is linked to an electron-withdrawing group which facilitates formation of the aziridinyl anion and prolongs its solution lifetime.[3] Aziridinyl anions devoid of an adjacent stabilizing substituent could be generated by desulfinylation or transmetalation[4] and by deprotonation when an activating substituent (electron-withdrawing group) is present on the aziridine ring nitrogen.[5] In the deprotonation of *N*-unactivated alkylideneaziridines, the neighbouring exocyclic double bond has been reported to play an important role in increasing the kinetic acidity of the aziridine hydrogens.[6]

In contrast to α-lithiated aryloxiranes,[7] α-lithiated arylaziridines have been little investigated and α-lithiated 2,3-diphenylaziridines not at all. Having recently discovered

† Dedicated to Prof. Francesco Naso of the University of Bari on the occasion of his 70th birthday.

(1) (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325. (b) Hodgson, D. M.; Bray, C. D.; Humphreys P. G. *Synlett* **2006**, 1−22. (c) For a special issue on oxiranyl and aziridinyl anions, see: *Oxiranyl and Aziridinyl Anions as Reactive Intermediates in Synthetic Organic Chemistry*, *Tetrahedron Symposia-in-Print*; Florio, S., Ed. *Tetrahedron* **2003**, *59*, 9693−9864.

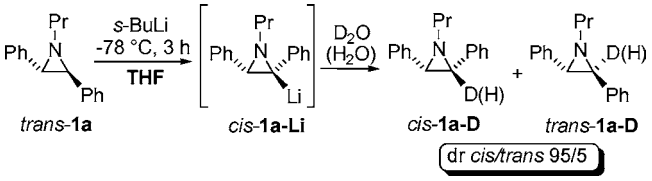
(2) (a) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, 247−258. (b) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347−1365. (c) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701−2743.

(3) (a) Alezra, V.; Bonin, M.; Mivouin, L.; Policar, C.; Husson, H. P. *Eur. J. Org. Chem.* **2001**, 2589−2594. (b) Luisi, R.; Capriati, V.; Florio, S.; Ranaldo, R. *Tetrahedron Lett.* **2003**, *44*, 2677−2681. (c) Yamauchi, Y.; Kawate, T.; Katagiri, T.; Uneyama, K. *Tetrahedron* **2003**, *59*, 9839−9847. (d) Luisi, R.; Capriati, V.; Florio, S.; Di Cunto, P.; Musio, B. *Tetrahedron* **2005**, *61*, 3251−3260. (e) Patwardhan, A. P.; Pulgam, V. R.; Zhang, Y.; Wulff, W. D. *Angew. Chem., Int. Ed.* **2005**, *44*, 6169−6172.

(4) (a) Satoh, T.; Ozawa, M.; Takano, K.; Kudo, M. *Tetrahedron Lett.* **1998**, *39*, 2345−2348. (b) Vedejs, E.; Little, J. *J. Am. Chem. Soc.* **2002**, *124*, 748−749.

10.1021/ol0700714 CCC: $37.00
Published on Web 03/06/2007

Scheme 1



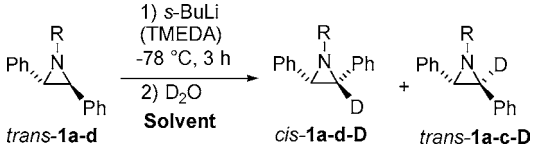
that monophenylaziridines undergo unexpectedly clean *ortho*-lithiation,[8] we decided to investigate the lithiation reaction of *cis*- and *trans*-*N*-alkyl-2,3-diphenylaziridines.

Treatment of the commercially available *N*-propyl-2,3-diphenylaziridine *trans*-**1a** with *s*-BuLi at −78 °C in THF furnished almost quantitatively the aziridine *cis*-**1a** and deuterated aziridine *cis*-**1a-D**, respectively, upon quenching with H_2O or D_2O (Scheme 1, Table 1). Taking into account that protonation or deuteration of organolithiums normally takes place with retention of configuration,[9] we assume that in THF the lithiated aziridine should be present as *cis*-**1a-Li**, with a configuration which is opposite to that of the starting aziridine *trans*-**1a**. (Scheme 1).

Similarly to the aziridine *trans*-**1a**, the lithiation−deuteration sequence of *N*-butylaziridine *trans*-**1b** and *N*-ethylaziridine *trans*-**1c** in THF gave [2-$^2H_1$]-aziridines *cis*-**1b-D** and *cis*-**1c-D** (Table 1). Lithiation of aziridine *trans*-**1d** was very slow, likely for steric reasons, and the deuterated aziridine *cis*-**1d-D** was obtained in only 10% yield.

Lithiation of *N*-alkyl-2,3-diphenylaziridines *trans*-**1a**−**c** in a nonpolar solvent was successively investigated. In contrast with the stereochemical outcome of the reactions conducted in THF, the lithiation−deuteration sequence of aziridines *trans*-**1a**−**c**, performed in hexane or toluene, proceeded with complete retention of configuration giving deuterated aziridines *trans*-**1a**−**c-D** (Table 1). Here again, in order to explain the stereochemical result, we propose that in toluene or hexane the lithiated intermediates should be *trans* configured. These results clearly indicate that the solvent determines the stereochemistry of the lithiation−deuteration sequence with interesting repercussion on the synthetic application.

Table 1. Lithiation−Deuteration Sequence of Aziridines *trans*-**1a**−**d**



aziridine **1**	solvent	R	*cis*-**1-D**, % D[a]	*trans*-**1-D**, % D[a]	dr[b,c] *cis*/*trans*
trans-**1a**	THF	*n*-Pr	*cis*-**1a-D**, 96	*trans*-**1a-D**, 98	95/5
trans-**1b**	″	*n*-Bu	*cis*-**1b-D**, 98	*trans*-**1b-D**, 98	98/2
trans-**1c**	″	Et	*cis*-**1c-D**, 99	*trans*-**1c-D**, 98	98/2
trans-**1d**	″	*i*-Pr	*cis*-**1d-D**, 98	*trans*-**1d-D**, 0[d]	100/0[d]
trans-**1a**	toluene[e]	*n*-Pr	*cis*-**1a-D**, −	*trans*-**1a-D**, 95	<2/98
trans-**1b**	″	*n*-Bu	*cis*-**1b-D**, −	*trans*-**1b-D**, 98	<2/98
trans-**1c**	″	Et	*cis*-**1c-D**, −	*trans*-**1c-D**, 97	<2/98

[a] Deuterium incorporation established by ESI−MS or GC−MS analysis on the molecular ion (see the Supporting Information). [b] Diastereomeric ratio (dr) was established by the analysis of the ^1H NMR spectra of the crude reaction mixtures. [c] Chemical yields were all >95%. [d] The conversion was only 10%; *trans*-**1d-D** was not detected, and 90% of unreacted starting material was recovered. [e] Hexane or Et_2O can be used as the solvent with no change in the stereoselectivity.

In order to evaluate the effect of the geometry of the investigated diphenylaziridines on the stereochemistry of the lithiation-trapping sequence, we studied the lithiation reaction of *N*-alkyl-2,3-diphenylaziridines *cis*-**1a**,**d**,**e** (alkyl = *n*-Pr, *i*-Pr, Me), disclosing that they do not undergo any lithiation upon treatment with alkyllithiums under varied experimental conditions in terms of solvent (THF, hexane, toluene), ligand (TMEDA), and temperature and were recovered unchanged after addition of D_2O or routine electrophiles.

NMR experiments proved to be particularly useful to explain the observed strikingly different reactivity of *cis*- and *trans*-2,3-diphenylaziridines toward lithiation. Our idea is that the nitrogen of the aziridine ring may be playing a role. A careful examination by NMR of the nitrogen configuration in *cis*- and *trans*-2,3-diphenylaziridines showed that *cis*-2,3-diphenylaziridines were all configurationally stable at the nitrogen:[10] indeed, the lone-pair and the two phenyl groups are *cis* each other with the two aziridine ring hydrogens on the opposite side, as established by NOESY correlations. In contrast, the 2,3-diphenylaziridines *trans*-**1a**−**d** show a slow nitrogen inversion on the NMR time scale (195 K) that makes the aziridine ring hydrogens diastereotopic, each of them being *cis* to the nitrogen lone-pair in the equilibrating topomers (Figure 1).[11−13]

With the assumption that a preliminary coordination of *s*-BuLi to the nitrogen lone-pair should be a prerequisite for

(5) (a) Vedejs, E.; Kendall, J. T. *J. Am. Chem. Soc.* **1997**, *119*, 6941−6942. (b) Bisseret, P.; Bouis-Peter, C.; Jacques, O.; Henriot, S.; Eustache, *Org. Lett.* **1999**, *1*, 1181−1182. (c) O'Brien, P.; Rosser, C. M.; Caine, D. *Tetrahedron* **2003**, *59*, 9779−9791. (d) Vedejs, E.; Bhaun Prasad, S. A.; Kendall, J. T.; Russel, J. S. *Tetrahedron* **2003**, *59*, 9849−9856. (e) Rosser, C. M.; Coote, S. C.; Kirby, J. P.; O'Brien, P.; Caine, D. *Org. Lett.* **2004**, *6*, 4817−4819. (f) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2005**, *7*, 1153−1156. (g) Hodgson, D. M.; Miles, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 949−952. (h) Moore, S. P.; Coote, S. C.; O'Brien, P.; Gilday, J. *Org. Lett.* **2006**, *8*, 5145−5148. (i) Hodgson, D. M.; Humphreys, P. G.; Ward, J. G. *Org. Lett.* **2006**, *8*, 995−998.

(6) (a) Hayes, J. F.; Prevost, N.; Prokes, I.; Shipman, M.; Slawin, A. M. Z.; Twin, H. *J. Chem. Soc., Chem. Commun.* **2003**, 1344−1345. (b) Montagne, C.; Prèvost, N.; Shiers, J. J.; Prié, G.; Rahman, S.; Hayes, J. F.; Shipman, M. *Tetrahedron* **2006**, *62*, 8447−8457.

(7) (a) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445−2448. (b) Florio, S.; Aggarwal, V.; Salomone, A. *Org. Lett.* **2004**, *6*, 4191−4194.

(8) Capriati, V.; Florio, S.; Luisi, R.; Musio, B. *Org. Lett.* **2005**, *7*, 3749−3752.

(9) (a) Faibish, N. C.; Park, Y. S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 11561−11570. (b) Derwing, C.; Frank, H.; Hoppe, D. *Eur. J. Org. Chem.* **1999**, 3519−3524.

(10) The barrier for the nitrogen inversion is expected to be higher in the *cis* isomer, and only one isomer, indeed, is seen. It is worth pointing out that the two invertomers of *cis*-configured aziridines should have different energies since the one that put the alkyl group *cis* to the phenyl rings is the less stable one.

(11) (a) Nagel, D. I.; Woller, P. B.; Cromwell, N. H. *J. Org. Chem.* **1971**, *36*, 3911−3917. (b) Martino, R.; Abeba, M. J.; Lattes, A. *J. Heterocycl. Chem.* **1973**, *10*, 91−94. (c) Pierre, J. L.; Baret, P.; Arnaud, P. *Bull. Soc. Chim. Fr.* **1971**, 3619−3628.

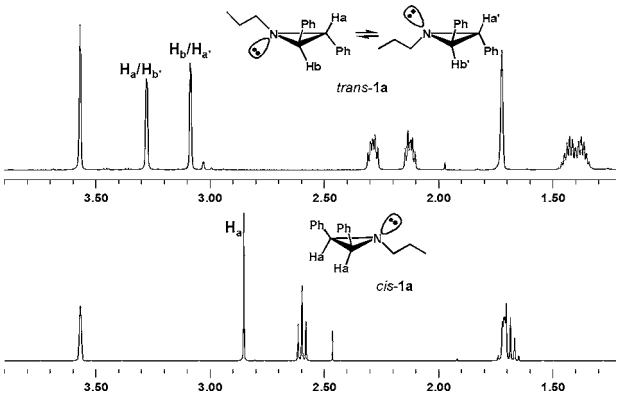
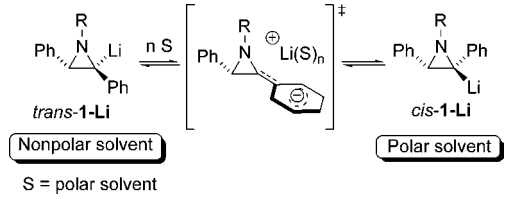


Figure 1. ^{1}H NMR spectra at 195 K in THF-d_8 of aziridines *cis*- and *trans*-**1a**.

the deprotonation to occur, only the trans isomer has the stereoelectronic requirement for the proton abstraction, while the protons of the *cis* isomer are too far from the base (the organolithium coordinated to the nitrogen lone pair) to be abstracted.[14] On the basis of this model, an explanation for the observed stereochemistry in the lithiation-deuteration sequence of *trans*-**1a**−**d** (inversion of configuration in THF, retention in hexane or toluene) might be that *trans*-**1-Li** should be the first lithiated intermediates formed. It is likely that in a polar solvent such as THF, lithiated species *trans*-**1-Li** might exist as contact ion-pairs that undergo isomerization, via a more polar transition state, to the *cis* counterparts (*cis*-**1-Li**) (Scheme 2), which are then trapped to give products

Scheme 2



with a configuration which is opposite to that of the starting aziridines.[15] Such a *trans* to *cis* isomerization, which has precedents with other aziridines,[16] can be accounted for with the higher thermodynamic stability of the *cis* isomer (the nitrogen lone-pair and the C−Li bond are trans each other in the *cis* isomer), as reported for other aziridines.[17] The same lithiated species *trans*-**1-Li** would not tend to isomerize in a nonpolar solvent such as hexane or toluene so that the trapping takes place with retention of configuration.[15,18]

The solvent effect was further investigated and it was found that also in diethyl ether the lithiation-deuteration sequence of *trans*-**1a** proceeds with retention of configuration either in the presence or absence of TMEDA, which, however, makes the deprotonation faster.

From a synthetic point of view, it was interesting that trapping of *trans*- and *cis*-**1a-Li** with a series of electrophiles furnished highly diastereoselectively functionalized *cis* aziridines in THF and *trans* isomers in hexane or toluene (Table 2). Specifically, in THF, high stereoselectivity was observed with most electrophiles giving *cis* aziridines **2a**−**j** from *trans*-**1a**;[19] a low stereoselectivity was observed with Bu_3SnCl where a 57:43 mixture of the two diastereomers **2e** and **3e** (98% yield) formed. It is well documented that the coupling reaction of organolithiums with organostannanes (R_3SnX) may proceed either with retention or inversion of configuration depending upon the nature of the organostannane with reference to the R groups and the leaving group.[20] Indeed, we found that in THF the reaction of *cis*-**1a-Li** with Me_3-SnCl (Table 2, entry 6) gave a mixture of *cis* and *trans* isomers **2f** and **3f** in a 85/15 ratio, whereas the reaction with bis(tributyltin)oxide furnished exclusively the corresponding *cis* isomer **2e** (dr >98/2) (Table 2, entry 5). This may be the result of a competition between a retentive (S_E2ret) and an invertive electrophilic substitution (S_E2inv).[21]

Instead, *trans* aziridines **3a**,**b**,**e**−**g** were prepared in a highly stereoselective manner when the lithiation-trapping sequence of *trans*-**1a** with the appropriate electrophile was performed in toluene or hexane. In some cases, the stereoselectivities were affected by the electrophile; a complete inversion of configuration was obtained in the reaction with Me_3SiCl (Table 2, entry 18) which may be ascribed to an S_E2inv mechanism.[21] A poor stereoselectivity was also observed when BnBr or allylBr (Table 2, entries 13 and 14) were used as the electrophile, likely because of a competing single-electron-transfer process.[22]

It was also found that when the lithiated aziridine, generated in toluene from *trans*-**1a**, was treated with a crown ether

(12) By dynamic ^{1}H NMR experiments performed in THF-d_8 on aziridine *trans*-**1a**, it was possible to study the nitrogen inversion. Aziridine *trans*-**1a** showed only one signal for the aziridine protons at 293 K; cooling down the sample to 195 K, a splitting into two lines for the above protons is observed testifying a slow nitrogen inversion. The reduced rate of inversion with respect to the NMR time scale makes the two aziridine protons diastereotopic and then distinguishable. No splitting was observed in the case of the corresponding *cis*-aziridine ring protons.

(13) Davies, M. W.; Shipman, M.; Tucker, J. H. R.; Walsh, T. R. *J. Am. Chem. Soc.* **2006**, *128*, 14260−14261.

(14) A complex-induced proximity effect could be operative in the α-lithiation of aziridines *trans*-**1a**−**d**; see: Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206−2225.

(15) Some spectroscopical evidences from an NMR investigation on these lithiated intermediates are in agreement with this hypothesis and results will be reported in due course; see also: Hoffmann, R. W.; Ruhl, T.; Chemla, F.; Zahneisen, T. *Liebigs Ann. Chem.* **1992**, 719−724.

(16) (a) Turner, A. B.; Heine, H. W.; Irving, J.; Bush, J. B. *J. Am. Chem. Soc.* **1965**, *87*, 1050−1055. (b) Lutz, R. E.; Turner, A. B. *J. Org. Chem.* **1968**, *33*, 516−518. (c) Coutrot, P.; Elgadi, A.; Grison, C. *Heterocycles* **1989**, *28*, 1179−1192.

(17) Haner, R.; Olano, B.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1676−1693.

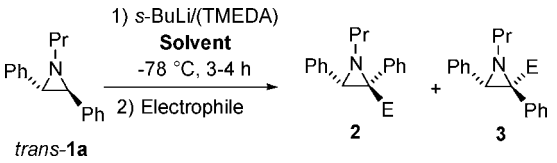
(18) Moreover, we cannot rule out that an equilibrium between two isomeric lithiated intermediates could be present and that this could be differently shifted depending on the solvent.

(19) Relative stereochemistry has been ascertained by NOESY 2D and 1D experiments; see the Supporting Information for details.

(20) Hammerschmidt, F.; Hanninger, A.; Simov, B. P.; Vollenkle, H.; Werner, A. *Eur. J. Org. Chem.* **1999**, 3511− 3518.

(21) For a recent report on the reactivity of α-amino-organolithiums, which are related to α-lithiated aziridines, see: Gawley, R. E.; Coldham, I. In *The Chemistry of Organolithium Compounds, Part 2*; Rappoport, Z., Marek, I., Eds.; Wiley & Sons: New York, 2004; pp 997−1052.

Table 2. Lithiation-Trapping Sequence of Aziridine *trans*-**1a**



entry	electrophile	solvent	aziridines **2, 3**	yield,[a] %	dr **2/3**[b]
1	MeI	THF	**2a**	98	>98/2
2	EtI	″	**2b**	92	>98/2
3	BnBr	″	**2c**	70	>98/2
4	allylBr	″	**2d**	92	>98/2
5	$(Bu_3Sn)_2O$	″	**2e/3e**	45	98/2[c]
6	Me_3SnCl	″	**2f/3f**	57	85/15
7	acetone	″	**2g/3g**	25[d,e]	90/10
8	Me_3SiCl	″	**2h**	98	98/2
9	6-bromo-1-hexene	″	**2i**	48	98/2
10	bromomethyl-cyclopropane	″	**2j**	38	98/2
11	MeI	toluene[f]	**3a**	64	<2/98
12	EtI	″	**3b**	95	<2/98
13	BnBr	″	**2c/3c**	98	50/50
14	allylBr	″	**2d/3d**	84	50/50
15	Bu_3SnCl	″	**3e**	80	<2/98
16	Me_3SnCl	″	**3f**	30	<2/98
17	acetone	″	**3g**	73	<2/98
18	Me_3SiCl	″	**2h**	70	98/2

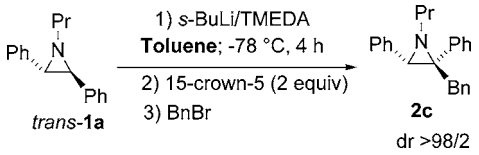
[a] Isolated yields. [b] Diastereomeric ratio (dr) ascertained by ^{1}H NMR on the crude reaction mixtures. [c] Bu_3SnCl was also used as the electrophile (see text). [d] Compounds **2g** and **3g** could be easily separated by flash chromatography. [e] A large amount of aziridine *cis*-**1a** was recovered as the result of an acid−base reaction with the electrophile. [f] Similar results were obtained when the reaction was performed in *n*-hexane.

(15-crown-5, 2 equiv) and then reacted with BnBr, *cis*-benzylated aziridine **2c** was obtained with high stereoselectivity (dr >98/2) as observed in THF (Scheme 3). Under such conditions, the lithium complexation by the crown ether would reduce the covalent character of the C−Li bond, as it should be in a nonpolar solvent such as toluene, thus promoting the thermodynamically favored *trans* to *cis* isomerization.

The trapping reaction of lithiated aziridine *trans*-**1a** was performed also with acetone giving the corresponding

(22) In an attempt to demonstrate the intervening of a SET mechanism, bromomethylcyclopropane and 6-bromo-1-hexene were used as radical scavengers (see: (a) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344−3350. (b) Gawley, R. E.; Eddings, D. B.; Santiago, M.; Vicic, D. A. *Org. Biomol. Chem.* **2006**, *4*, 4285−4291) in the trapping reaction of *trans*-**1a-Li** in toluene and hexane as the solvents. A complex reaction mixture was obtained in both cases. Only a small amount of the desired alkylated products was observed from a GC−MS analysis.

Scheme 3



hydroxyalkylated aziridines **2g** in THF (dr = 90/10) and **3g** in toluene (dr >98/2).

In conclusion, in this paper, we report for the first time that "unactivated" *trans*-*N*-alkyldiphenylaziridines undergo exclusive α-lithiation with a stereochemistry which depends upon the coordinating ability of the solvent (complete inversion of configuration in THF or toluene/crown ether and retention in hexane, toluene or diethyl ether). A different geometry, *cis* or *trans*, of the involved lithiated aziridines (*cis*-**1-Li** and *trans*-**1-Li**) in polar and nonpolar solvents is proposed to explain the observed opposite stereochemistry on going from THF (or toluene/crown ether) to hexane or ether or toluene. For the α-lithiation to occur we propose a model where the nitrogen lone-pair must sit *cis* to the aziridine ring hydrogens. This explains why the *cis*-*N*-alkyldiphenylaziridines, existing exclusively as the invertomers that put the ring hydrogens far away from the nitrogen lone-pair, do not undergo any lithiation. It is useful from the synthetic point of view that the regioselective and stereoselective lithiation of *trans*-*N*-alkyldiphenylaziridines can be used for the preparation of variously substituted stereodefined diphenylaziridines, which are potentially very attractive for their biological activity[23] and spectroscopic properties and for their utility as building blocks for the synthesis of target molecules.[24]

Acknowledgment. This work was carried out under the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" by the University of Bari and by the Interuniversities Consortium CINMPIS. We thank Prof. Reinhard W. Hoffmann of the University of Marburg for the useful discussion.

Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0700714

(23) (a) Kadaba, P. K.; Dahlman, D. L. U.S. Patent No. 4,582,827, 1986; *Chem. Abstr*. **1986**, *105*, 56366. (b) Chang, W.-H.; Piccirilli, R. U.S. Patent No. 4,528,333, 1985; *Chem. Abstr*. **1985**, *103*, 105744.

(24) Urbaniak, K.; Szymanski, R.; Romanski, J.; Mloston, G. *Helv. Chim. Acta* **2004**, *87*, 496−510.