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NOTE

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BH_3-Promoted Stereoselective β-Lithiation of *N*-Alkyl-2-phenylaziridines

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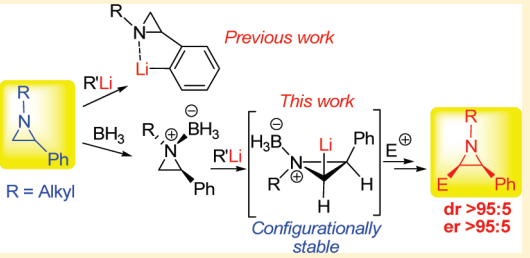
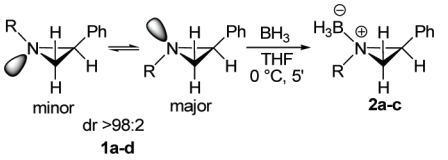
Supporting Information

ABSTRACT: BH_3 complexes of *N*-alkyl-2-phenylaziridines have been synthesized and their structure and stereochemistry proved with DFT calculations and NMR experiments. It has been demonstrated that the Lewis acid complexation is able to promote a regioselective β-lithiation in 2-phenylaziridino−borane complexes. The lithiated intermediates were configurationally stable, allowing an enantioselective preparation of *cis*-2,3-disubstituted aziridines.



Aziridines are widely used as versatile building blocks for the synthesis of a variety of biologically and pharmaceutically important molecules.[1] Several methods for the synthesis of aziridines have been developed, and their use as chiral building blocks has also emerged recently.[2] In the past decade, much interest has been devoted to the development of new methodologies for a regioselective lithiation and functionalization of such substrates.[3] Data from the literature indicate that *N*-alkyl-2-phenylaziridines undergo smooth *ortho*-lithiation, thus showing the ability of the aziridino group to act as a directing metalation group (DMG).[4] In contrast, *trans*-*N*-alkyl-2,3-diphenylaziridines undergo exclusive α-lithiation with a stereochemistry strongly depending on the coordinating ability of the solvents.[5,6] These results have been rationalized, taking into account the crucial role of the aziridine nitrogen dynamics in controlling the α- versus *ortho*-lithiation competition.[7] Focusing on the deprotonation of simple *N*-alkyl-substituted aziridines, Vedejs[8] reported the lithiation of a simple unsubstituted aziridine by using BH_3 activation, a procedure originally developed by Kessar[9] to promote the α-metalation of tertiary amines. A stereochemical analysis of the reaction was consistent with a dominant aziridine lithiation *syn* to the BH_3 group.[10] Starting from this evidence, and conscious that *N*-alkyl-2-phenylaziridines undergo exclusive *ortho*-lithiation, we decided to investigate the lithiation of the corresponding BH_3 complexes lacking the nitrogen lone pair availability. We started our investigation with a careful structural and stereochemical analysis, by NMR and DTF calculations, on the BH_3 complexes of *N*-alkyl-2-phenylaziridines. 2-Phenylaziridines **1a**−**d** were prepared according to a known procedure[11] and reacted with a 1 M THF solution of BH_3·THF complex (Table 1). The corresponding aziridino−borane complexes **2a**−**c** were obtained as single diastereoisomers in high yields, while attempts to prepare the borane complex of the trityl aziridine **1d** were unsuccessful.[12]

Table 1. Synthesis of the Aziridino−Borane Complexes 2a−c



aziridine **1**	R	borane complex **2**	yield[a] (%)
1a	*t*-Bu	**2a**	>95
1b	Et	**2b**	>95
1c	$Ph(CH_3)_2C$	**2c**	92
1d	$(Ph_3)_3C$	**2d**	*b*

[a] Determined on pure isolated products. [b] The complex was not enough stable for isolation.

Before evaluation of the structural analysis of the aziridino−borane complexes, some stereochemical considerations are needed. If one considers that *N*-alkyl-2-phenylaziridines could undergo nitrogen inversion, two diastereoisomers should, in principle, be expected in the reaction with BH_3. Nevertheless, previous reports demonstrated that, in *N*-alkylmonophenylaziridines, the main diastereoisomer is the one that sets the lone pair on the same side of the phenyl ring (dr >98:2).[4−7] With this assumption in mind, the stereochemistry of BH_3-coordinated *N*-alkyl-2-phenylaziridines was assigned, taking into account the results of NMR experiments and DFT calculations. Table 2 reports experimental, calculated, and scaled ^1H and ^{13}C NMR chemical shifts (ppm) for complexes **2a** and **2b** bearing the phenyl group and the BH_3 group in a *cis* relationship. For

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Table 2. Experimental, Calculated, and Scaled ^{1}H and ^{13}C NMR Chemical Shift (ppm)

	2a			2b			inv-2b
atom	δ_{exp} [a]	$\delta_{MPW1PW91}$ [b]	δ_{B3LYP} [c]	δ_{exp} [a]	$\delta_{MPW1PW91}$ [b]	δ_{B3LYP} [c]	δ_{B3LYP} [c]
C_1	44.38	48.71 (44.94)	50.70 (46.03)	48.77	57.05 (53.65)	59.40 (54.64)	58.53 (53.30)
C_2	35.96	37.51 (35.26)	38.82 (34.64)	40.99	38.83 (36.31)	39.81 (35.98)	39.29 (35.35)
C_7	60.69	64.45 (60.94)	69.53 (64.08)	59.33	62.81 (59.14)	65.08 (60.05)	54.36 (49.41)
C_8	132.01	139.25 (132.25)	141.30 (132.8)	11.85	13.52 (12.20)	13.80 (11.21)	13.64 (11.42)
C_{13}	129.96	137.50 (130.58)	138.22 (129.94)	130.87	138.73 (131.45)	140.73 (132.10)	139.47 (128.80)
C_{14}/C_{18}	127.90	134.23 (127.47)	135.04 (126.89)	129.89	137.49 (130.27)	138.31 (129.79)	138.02 (127.44)
C_{15}/C_{17}	128.29	134.76 (127.97)	135.51 (127.34)	127.85	134.42 (127.34)	135.24 (125.92)	136.38 (125.92)
C_{16}	26.27	27.33 (25.56)	27.68 (23.95)	128.59	135.20 (128.09)	136.05 (127.64)	136.59 (126.11)
R^2		0.999	0.998		0.997	0.996	0.997
MAE		4.78	6.40		5.53	6.58	6.44
CMAE		0.45	1.44		1.50	2.05	1.94
H_4	3.70	3.88 (3.79)	3.84 (3.79)	3.34	3.54 (3.50)	3.51 (3.49)	4.06 (3.62)
H_5	2.63	2.41 (2.61)	2.42 (2.46)	2.43	2.35 (2.40)	2.36 (2.42)	2.40 (2.41)
H_6	2.66	2.69 (2.69)	2.64 (2.67)	2.82	2.58 (2.62)	2.57 (2.62)	2.44 (2.44)
CH_3	1.40	1.38 (1.48)	1.37 (1.48)	1.45	1.39 (1.52)	1.39 (1.51)	1.24 (1.56)
R^2		0.979	0.984		0.963	0.964	0.889
MAE		0.10	0.10		0.14	0.14	0.34
CMAE		0.06	0.09		0.11	0.11	0.20

[a] Experimental values in $CDCl_3$ at 298 K. [b] PCM/MPW1PW91/6-311++G(d,p) calculation, scaled values in parentheses. [c] PCM/B3LYP/6-311++G(d,p) calculations, scaled values in parentheses.

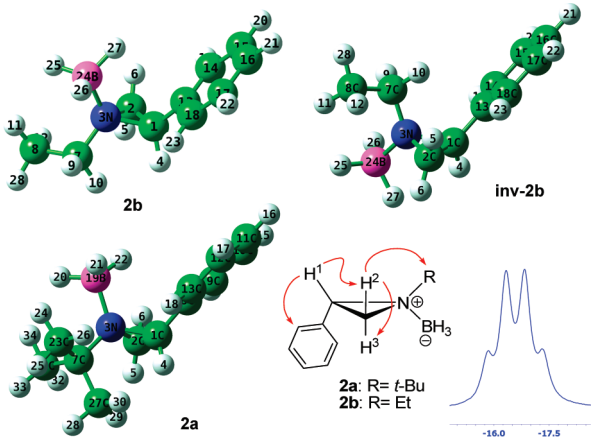

Figure 1. Equilibrium geometries (in $CDCl_3$) at the PCM/B3LYP/6-311++G(d,p) level for complexes **2a**, **2b**, and **inv-2b**, experimental main NOE interactions and ^{11}B NMR (192 MHz) of complexes **2a,b**.

comparison, the theoretical data of the diastereoisomeric complex **inv-2b**, bearing the phenyl and the BH_3 groups *trans* to each other, were also evaluated. The equilibrium geometries at the DFT-B3LYP/6-311++G(d,p) level of complexes **2a**, **2b**, and **inv-2b** are reported in Figure 1.

Chemical shift calculations were performed by employing the gauge-invariant atomic orbital (GIAO) method implemented in Gaussian 03 programs at the DFT-B3LYP/6-311++G(d,p) and DFT-MPW1PW91/6-311++G(d,p).[13,14] To take into account the medium effect, we performed the calculations considering the chloroform effect within the polarization continuum model (PCM).[15] The NMR chemical shifts (δ) were calculated as the differences of isotropic shielding constants (σ) with respect to the TMS (tetramethylsilane) reference.[16] The parameters employed to evaluate the quality of the theoretical prediction, and to discriminate between the possible structures, are the last-squares linear fitting parameter (R^2) of the correlation plots between computed (without scaling) and experimental data, the mean absolute error (MAE), and the corrected mean absolute error (CMAE).[17,18] All of the calculated data are reported in Table 2, and they are in good agreement with the experimental data of complexes **2a** and **2b**. A better correlation, between experimental and calculated chemical shifts, has been observed by using the MPW1PW91 functional with respect to the B3LYP functional. In addition, ^{13}C chemical shifts calculated at the B3LYP/6-311++g(d,p) level of theory are unreliable to distinguish between **2b** and **inv-2b**.[19] Nevertheless, a better fit with the experimental chemical shifts of **2b** was found by comparison of calculated ^{1}H chemical shifts of **2b** with respect to **inv-2b**. In this case, the results of calculations are more reliable to assign the correct structure as clearly indicated by the corresponding R^2, MAE, and CMAE values. Furthermore, the geminal and vicinal spin−spin coupling constants (SSCC) between the aziridinyl protons of complexes **2a**, **2b**, and **inv-2b** have been calculated at the B3LYP/6-311++G(d,p) level (Table 3). In this case, a very good correlation was found in the analysis of calculated and experimental values, confirming the well-known trend observed for the aziridinyl ring: $J_{cis} > J_{trans} \gg J_{gem}$.

Table 3. Experimental and Calculated SSCC $^{2,3}J_{HH}$

	2a		2b		inv-2b
SSCC [a]	exp	B3LYP [b]	exp	B3LYP [b]	B3LYP [b]
J_{cis}	7.8	7.7	7.5	7.3	6.5
J_{trans}	6.3	4.9	6.3	5.1	4.9
J_{gem}	2.1	1.9	2.1	2.1	2.0

[a] Values in hertz. [b] At PCM/B3LYP/6-311++G(d,p) level.

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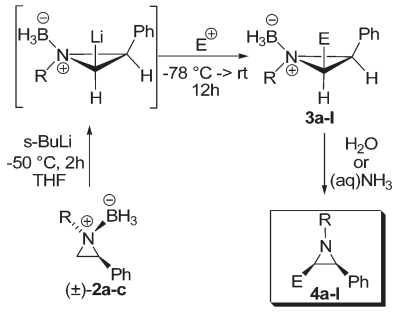
Table 4. Lithiation/Electrophile Trapping Sequence of Aziridino−Borane Complexes 2a−c



entry	R	E^+	aziridine 4	yield[a] (%)
1	*t*-Bu	D_2O	**4a**	>95[b,c]
2	*t*-Bu	D_2O	**4a**	>95[b,d]
3	*t*-Bu	D_2O	**1a**	*e*
4	*t*-Bu	CH_3I	**4b**	80[b] (78)[f]
5	*t*-Bu	$(CH_3)_3SiCl$	**4c**	>95[b]
6	*t*-Bu	$(CH_3)_2CO$	**4d**	73 (69)[f]
7	*t*-Bu	$(CH_3)_3CCHO$	**4e**	86[g]
8	Et	D_2O	**4f**	>95[b]
9	Et	CH_3I	**4g**	60
10	Et	$(CH_3)_3SiCl$	**4h**	72
11	Et	$(CH_3)_2CO$	**4i**	68 (63)[f]
12	Et	$(CH_3)_3CCHO$	**4j**	48[g]
13	$Ph(CH_3)_2C$	D_2O	**4k**	>95[b]
14	$Ph(CH_3)_2C$	CH_3I	**4l**	56

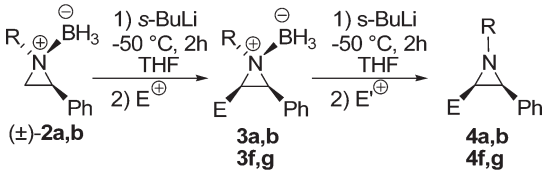
[a] Isolated yields. [b] Ascertained by ^1H NMR spectroscopy of the crude reaction mixture. [c] Reaction performed in THF. [d] Reaction performed in Et_2O [e] Reaction performed in hexane. Only starting material was recovered. [f] Yield obtained under one-pot reaction conditions. [g] A single diastereoisomer was obtained (stereochemistry at the newly created stereogenic center not assigned).

By this DFT analysis, we can conclude that on the basis of calculated ^1H chemical shifts and the predicted SSCC one could be able to discriminate between very similar structures such as diastereoisomers **2b** and **inv-2b**. The computational results were finally confirmed by ^{11}B NMR and NOE experiments on borane complexes **2a,b** (see the Supporting Information). In the ^{11}B NMR the quartet was found, for the BH_3 group, around −16.6 ppm (referenced to $BF_3 \cdot Et_2O$) as expected for tetracoordinated boron.[20] NOE experiments showed spatial correlations consistent with a syn relationship between the phenyl ring and the BH_3 group (Figure 1).

Once the structure of aziridino−borane complexes was established, their reactivity with organolithiums was evaluated. Lithiations were performed as reported in Table 4, and the optimal reaction conditions were found using aziridino−borane complex **2a**. When **2a** was reacted with *s*-BuLi (1.2 equiv) in THF at −50 °C for 2 h, the corresponding aziridinyllithium was generated as proved by its trapping with D_2O to furnish complex **3a**. BH_3 removal was easily achieved by adding a small amount of H_2O at room temperature.

After the workup, the corresponding 2-deuterated aziridine **4a** was recovered almost quantitatively and as a single stereoisomer (Table 4, entry 1). By comparison of ^1H NMR spectra of **1a** and **4a**, the syn relationship between the phenyl group and the deuterium on the β-carbon was established. By assuming that the reaction at the lithiated carbon occurs with retention of configuration, this finding strongly suggests that metalation occurred exclusively syn to the BH_3 moiety as reported for other aziridino−borane complexes.[10]

Scheme 1. Attempts for Double Functionalization on Complexes 2a,b



Comparable results were obtained when Et_2O was used as the reaction solvent, while no reaction was observed in hexane (Table 4, entries 2 and 3, respectively).

As an extension, the lithiation/trapping sequence of **2a** was executed using several electrophiles. The reactions occurred with high regio- and stereoselectivity furnishing, after removal of the BH_3 group, *cis*-2,3-disubstituted aziridines **4b**−**e** (Table 4, entries 4−7). The lithiation/electrophile trapping of borane complexes **2b,c** under the optimal reaction conditions (Table 4, entries 8−14) furnished similar results. However, it is worth noting that BH_3 removal from *N*-ethyl-substituted aziridines **3f**−**j** proved to be more problematic, needing hot 28% aqueous NH_3 for several hours (see the Supporting Information). In the case of *N*-cumyl-substituted aziridines **3k**−**l**, the BH_3 removal was easily achieved by addition of few drops of H_2O at room temperature, a procedure leading to an immediate and vigorous evolution of gas from the reaction mixtures. These results strongly suggest that steric demand of the aziridine nitrogen substituent could affect the strength of N−B bond. The *cis* stereochemistry of the aziridines **4a**−**l** was easily ascertained by evaluating the ^1H NMR ^3J coupling constants for the aziridinic protons ($J_{cis} > J_{trans}$) and in some cases confirmed by NOE experiments (see the Supporting Information).

The possibility to perform the BH_3-complexation/lithiation/electrophile trapping/BH_3 removal sequence under one pot conditions was also pursued. Aziridines **1a,b** were first converted into the corresponding complexes **2a,b** and reacted with *s*-BuLi for 2 h and then with the electrophile (Scheme 1). The reaction mixture was subjected to BH_3 removal to obtain free aziridines **4b**, **4d**, and **4i** (Table 4, entries 4, 6, and 11).[21,22]

When deuterated and methylated borane complexes **3a,b** and **3f,g** underwent lithiation with *s*-BuLi followed by the addition of the electrophile and BH_3 removal, only aziridines **4a,b** and **4f,g** were recovered. Similar results were obtained by performing the full sequence under one-pot conditions starting from complexes **2a,b** (Scheme 1).

Moreover, in order to verify the configurational stability of this kind of lithiated aziridino−borane complexes, of great importance for a stereoselective synthesis of aziridines and derivatives,[23] the enantioenriched complex (*S,S*)-**2b** was prepared (er >95:5) and reacted with *s*-BuLi under the optimized reaction conditions (Scheme 2).

The corresponding aziridinyllithium reacted with retention of configuration with D_2O and Me_3SiCl to furnish the corresponding borane complexes (*S,S,R*)-**3f** and (*R,S,R*)-**3h**. Trapping with benzophenone occurred again with retention of configuration,

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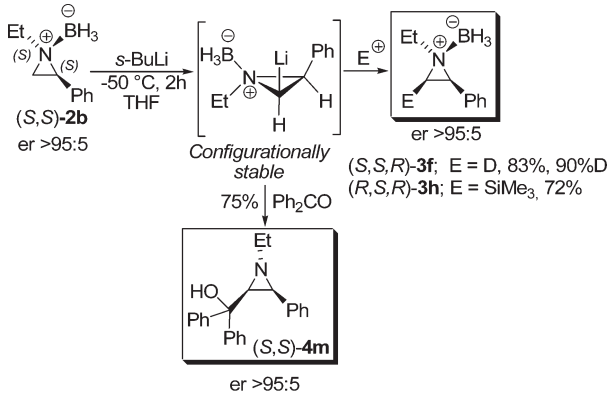
Scheme 2. Evaluation of the Configurational Stability of Lithiated Aziridino−Borane Complexes



but the introduced hydroxyalkyl group likely promotes the BH_3 removal to produce aziridine (*S*,*S*)-**4m**. However, all of the products were found to be highly enantioenriched (er >95:5).[24] The observed configurational stability is in accordance with the results reported by Vedejs[10a] and Concellon[10b,c] and once more proves the role of the BH_3 group in promoting a syn lithiation, likely by an electrostatic complex induced proximity effect (CIPE).[25] In conclusion, the preparation of new *N*-alkyl-2-phenylaziridino−borane complexes has been accomplished, and their structure and reactivity have been evaluated. By using DFT analysis and NMR experiments, the structure and stereochemistry of the aziridino−borane complexes can be safely assessed and the model for calculations can be useful for predictions in similar systems. Concerning the reactivity of aziridino−borane complexes, a regio- and stereoselective lithiation at the terminal *β-cis* position, with respect to the α-benzylic position, has been observed.[26] It has been also demonstrated that the lithiated aziridino−borane complex is configurationally stable allowing the enantioselective synthesis of *cis*-2,3-disubstituted *N*-alkylaziridines. A final evidence is the switch of the regioselectivity in the lithiation of *N*-alkylmonophenylaziridines which are preferentially ortho lithiated in the absence of the BH_3 group.

EXPERIMENTAL SECTION

General Procedure for the Lithiation of Aziridino−Borane Complexes. A solution of *s*-BuLi (1.2 equiv, 1.4 M in cyclohexane) was added under inert atmosphere at −50 °C to a stirred solution of (*S*,*S*)-**2b** (3.11 mmol) in dry THF (7 mL). The reaction mixture was stirred at −50 °C for 2 h and then cooled at −78 °C before addition of Me_3SiCl (1.4 equiv, 4.35 mmol). The reaction mixture was then allowed to warm to room temperature and stirred until substrate consumption (TLC monitoring). The reaction mixture was poured into H_2O and extracted with CH_2Cl_2 (3×15 mL). The organic layers were dried under Na_2SO_4, and the solvent was evaporated in vacuo. Aziridino−borane (*S*,*R*,*R*)-**3h** was purified by crystallization from hexane.

(*R*,*S*,*R*)-**3h**: 95%; white solid; mp 65−67 °C; ^{1}H NMR (400 MHz, CD_3OD) δ 1.19 (s, 9 H), 1.46 (t, J = 7.1 Hz, 3 H), 1.63 (d, J = 9.6 Hz, 1 H), 2.84 (dq, J = 14.1, 7.1 Hz, 1 H), 2.94 (dq, J = 14.3, 7.1 Hz, 1 H), 3.54 (d, J = 9.6 Hz, 1 H), 7.31−7.35 (m, 3 H), 7.45−7.46 (m, 2 H); ^{13}C NMR (100 MHz, CD_3OD) δ 0.1, 12.3, 45.8, 53.1, 64.2, 127.7, 128.0, 129.5, 132.8; ^{11}B NMR (192 MHz, $CDCl_3$) δ −17.3 (q, J = 91 Hz); FT-IR (film, cm^{-1}) ν 3062, 3031, 2954, 2428, 2357, 2277, 1381, 1249, 1165, 843; ESI-MS m/z 256 $[M + Na]^+$ (100); $[\alpha]^{20}_D$ +61 (c 0.5, EtOH), er = 95:5. Anal. Calcd for $C_{13}H_{24}BNSi$: C, 66.95; H, 10.37; N, 6.01. Found: C, 66.84; H, 10.42; N, 6.08. Enantiomeric purity determined by HPLC analysis (Cellulose LUX-2 chiral column, hexane−*i*-PrOH 99.95:0.005, 0.5 mL/min, 227 nm, for racemic **3h**: t_1 = 15.93 min, t_2 = 17.67 min; for (*R*,*S*,*R*)-**3h** major t = 16.05 min, minor t = 17.5 min.

ASSOCIATED CONTENT

Supporting Information. Experimental details and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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DEDICATION

Dedicated to Prof. Saverio Florio on the occasion of his 70th birthday.

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