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Stereocontrolled lithiation/trapping of chiral 2-alkylideneaziridines: investigation into the role of the aziridine nitrogen stereodynamics†

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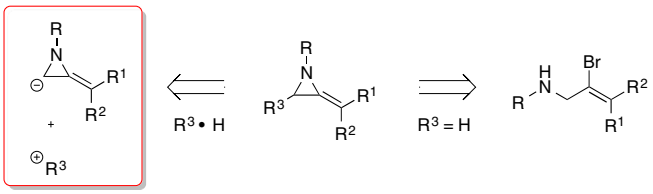
The origin of the stereoselectivity in the lithiation/trapping of 2-alkylideneaziridines bearing a chiral group as the nitrogen substituent, has been investigated. Optimal reaction conditions have been discovered by *in situ* FT-IR monitoring. In addition, it has been found that the solvent and the alkene substitution pattern are important factors able to impart a switch in stereoselectivity. While lithiation of the alkylidenaziridine ring flanked by either a fully substituted or a Z-configured alkene pendant occurs stereoselectively in THF, in contrast unsubstituted 2-methyleneaziridine gives lithiation in toluene with the opposite sense of stereoinduction. Lithiation experiments, on deuterium labelled 2-alkylideneaziridines, confirmed the configurational stability of the lithiated intermediates. A model based on complexation and proximity effects has been proposed to rationalize the reactivity. This model assumes that slowly equilibrating *N*-invertomers undergo deprotonation (lithiation) with different rates and that the stereochemical outcome is established during the deprotonation step.

Introduction

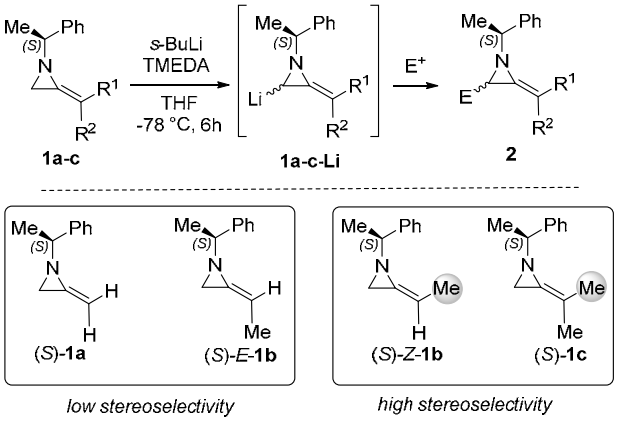
Aziridines are important building blocks in organic synthesis, and much research over the past few decades has been devoted to the development of effective synthetic methodologies for their preparation.[1] A special class of functionalized aziridines is represented by 2-alkylideneaziridines. These highly strained three-membered heterocycles possess a rich and varied chemistry.[2] For example, 2-methyleneaziridines participate in multi-component reactions,[3] Lewis acid promoted [3+2] and [4+3] cycloadditions,[4] oxidative rearrangements,[5] radical cascades,[6] and a growing number of transition metal catalysed processes.[7] An effective method for the preparation of these *N*-heterocycles relies on the intramolecular cyclization of readily available 2-bromoallylamines with sodium amide in liquid ammonia.[8] Whilst this method tolerates substantial variation in the substitution pattern of the methyleneaziridine framework, it is not suitable for the synthesis of derivatives bearing substituents at C–3 (i.e. $R^3 \neq H$). A potentially simple method to make such derivatives exploits the aziridinyl anion strategy[9] wherein C–3 of the 2-methyleneziridine is functionalized through deprotonation, with a suitable base, followed by trapping with an electrophilic species (Scheme 1).[10] Using this method, Shipman and coworkers accessed functionalized aziridines bearing different substituents on the aziridine nitrogen and at the double bond.[4a,4c,11] Using alkylideneaziridines bearing a chiral group as the N-substituent, the stereoselectivity of this lithiation/functionalization sequence was addressed and it was found that the stereoselectivity of this process was dependent on the geometry (i.e. *E* or *Z*) and the pattern of substituents on the alkene double bond.[12] Here we report detailed optimization studies, including in situ FT-IR experiments, that provide a better mechanistic understanding of the process, and reaction conditions that can deliver improved levels of stereocontrol.



Scheme 1. Overview of strategies to 2-alkylidineaziridines.

Results and discussion

To begin our investigation, the previously obtained results with chiral non-racemic aziridines **1a-c** were considered.[12] As reported in Scheme 2, upon electrophilic trapping of lithiated methyleneaziridines **1a-c-Li** a new stereogenic centre is created, and a mixture of diastereomers results. Moreover, it was observed that high levels of stereoselectivity (dr >93:7) could be achieved only with a substituent installed on the double bond as in the case (*S*)-*Z*-**1b** and (*S*)-**1c**. Curiously, with aziridine (*S*)-*E*-**1b** despite the presence of an alkene substituent, a lower level of stereoselectivity resulted. Similarly low levels of stereocontrol were seen in the case of unsubstituted aziridine (S)-**1a**. Such evidence prompted us to assume that a cis-relationship between the aziridine nitrogen and the substituent R^1 was a requirement for high stereoselectivity (Scheme 2). However, we felt that further experimentation with respect to the reaction parameters (i.e. ligand, temperature, solvent, time etc.) was merited to determine if the stereoselectivity of the lithiation of aziridines (S)-**1a** and (*S*)-*E*-**1b** could be improved.

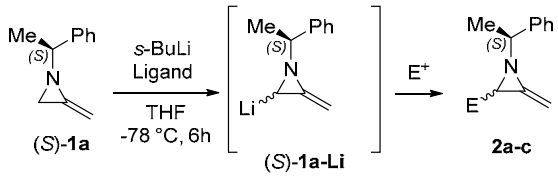


Scheme 2. Observed stereoselectivity in the lithiation/trapping sequence of alkylideneaziridines.

First the effect of the ligand N,N,N',N'-tetramethylethylen-diamine (TMEDA) was investigated and the obtained results were reported in Table 1. Aziridine (*S*)-**1a** was lithiated either in the presence or absence of TMEDA and the resulting

lithiated intermediates trapped with electrophiles. The diastereomeric ratios were ascertained by ^{1}H-NMR analysis of the crude reaction mixtures, and compared with those obtained under the previously optimized condition that is in the presence of the ligand. Aziridinyllithium (*S*)-**1a-Li** proved to be chemically stable over a period of several hours even in the absence of TMEDA; indeed, it could be quenched with deuterium furnishing aziridine (*S*)-**1a-D** almost quantitatively (95% D) and without decomposition (Table 1, entries 1,2). The lithiated intermediate also reacted with different electrophiles to give products **2a-c** with good yields either in the presence or absence of TMEDA (Table 1, entries 3-8). Because the same diastereoselectivity was observed working either in the presence or in the absence of TMEDA, it is reasonable to assume that the ligand is not playing an important role. Therefore, all the subsequent studies were performed without this additive.

Table 1. Effect of the ligand on the stereoselectivity of the lithiation/trapping sequence of (*S*)-**1a**.

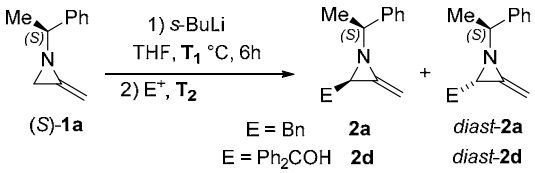


entry	TMEDA (equiv.)	E^+	product[a]	conversion (%)	dr[c,d]
1	1.2	CD_3OD	(*S*)-**1a-D**[b]	83	80/20
2	-	CD_3OD	(*S*)-**1a-D**[b]	>98	80/20
3	1.2	BnBr	**2a**/*diast*-**2a**	90	70/30
4	-	BnBr	**2a**/*diast*-**2a**	>98	70/30
5	1.2	Me_3SiCl	**2b**/*diast*-**2b**	90	80/20
6	-	Me_3SiCl	**2b**/*diast*-**2b**	90	80/20
7[d]	1.2	MeI	**2c**/*diast*-**2c**	87	70/30
8[d]	-	MeI	**2c**/*diast*-**2c**	67	70/30

[a]Aziridines **2a-c** were obtained as a mixture of inseparable diastereomers; [b]purification by distillation; [c]The dr values were determined by ^{1}H NMR analysis on the crude reaction mixture; [d]Assumed as (*S*,*R*)/(*S*,*S*) diastereomeric ratio (**2**/*diast*-**2**).

The reaction temperature was the next parameter investigated. The lithiation reactions of (*S*)-**1a** were performed under the conditions reported in Table 2. Benzyl bromide and benzophenone were used as the electrophile. The stereochemistry for the adducts **2a**,**d** and *diast*-**2a**,**d** were assigned by analogy to those of **2e** and **2f** whose stereochemistries have been deduced previously by X-ray diffraction (*vide infra*).[13] The lithiated intermediates were found to be chemically stable over a range of temperatures between –98 °C and –42 °C (Table 2). In the trapping reactions with benzyl bromide (entries 1-6), the stereoselectivity of the reactions was dependent on both the temperature T_1 for the generation of the lithiated aziridine, and temperature of quenching T_2: the lower the temperature, the higher the diastereoselectivity. Moreover, a switch in diastereoselectivity occurs upon generation and/or trapping at higher temperatures (Table 2, entries 4-5). We ascribe this behaviour to the electrophile; benzyl bromide is known to react with lithiated species with both retention and inversion of configuration.[14] The possibility of a temperature promoted radical pathway (by SET) is also not ruled out. When a warm/cool protocol was applied, achieved by warming the solution to –42 °C for 30 min followed by trapping with BnBr at –78 °C, no inversion of the diastereoselectivity was observed (entry 6). Using benzophenone as the electrophile, which reacts predominantly with retention of configuration,[15] little change in stereoselectivity was observed over a range of lithiation/quenching temperatures (entries 7-10). We conclude that lightly improved stereoselectivity can be observed by running these reactions at temperature as low as –98 °C.

Table 2. Effect of the temperature on the stereoselectivity of the lithiation/trapping sequence of (*S*)-**1a**.



entry	E^+	T_1 (°C)[a]	T_2 (°C)[b]	conversion (%)	dr **2**/*diast*-**2**[c]
1	BnBr	–78	–78	>98	70:30
2	BnBr	–78	–98	73	88:12
3	BnBr	–98	–98	94	83:17
4	BnBr	–78	–42	93	30:70
5	BnBr	–42	–42	50	30:70
6	BnBr	–78	–42 → –78[d]	50	75:25
7	Ph_2CO	–78	–78	>98	80:20
8	Ph_2CO	–78	–98	85	80:20
9	Ph_2CO	–78	–42	85	87:13
10	Ph_2CO	–98	–98	90	90:10

[a]T_1 is the lithiation temperature. [b]T_2 is the temperature of the trapping with the electrophile. All the reactions were kept for 30 min. at T_2 before addition of the electrophile. [c]Diastereomeric ratio calculated by ^{1}H NMR of the crude reaction mixture. [d]The lithiated intermediate was stirred at –42 °C for 30 min. and cooled to –78 °C before quenching.

To explore the influence of reaction time, we monitored the lithiation of aziridines (*S*)-**1a** and (*S*)-**1c** by *in situ* FT-IR.[16,17] This was done by monitoring the stretching vibration of the exocyclic C=C double bond during the course of the reaction. In neutral aziridine (*S*)-**1a**, this signal was detected at 1780 cm^{-1} in 0.2 M THF solution at –78 °C (Figure 1). Upon addition of *s*-BuLi, a new band at 1710 cm^{-1}, assigned to the lithiated intermediate (*S*)-**1a-Li**, appeared. The transformation was complete within 30 min with no further changes observed after 1 h. Upon addition of CD_3OD as deuterium source, aziridine (*S*)-**1a-D** was obtained in 80/20 diastereomeric ratio (98% D) confirming that the detected signal belongs to the lithiated intermediate (Figure 1). Similarly, in the lithiation of aziridine (*S*)-**1c** in THF, the signal for the stretching of the C=C double bond at 1810 cm^{-1} quickly disappeared upon addition of *s*-BuLi, and a new signal, likely belonging to lithiated aziridine (*S*)-**1c-Li** appeared at 1760 cm^{-1} (Figure 1). From these experiments, we conclude that these lithiations are complete within 30 min at –78 °C in THF. Trapping of (*S*)-**1c-Li** with benzophenone furnished the expected adduct **2f** as the major diastereomer (dr = 95:5) in 80% yield. The lithiation of (*S*)-**1c** was also undertaken in toluene, and was complete within 30 min, as ascertained by in-situ FT-IR monitoring. Moreover, quenching of (*S*)-**1c-Li** with benzophenone furnished a mixture of diastereomeric aziridines **2f** and *diast*-**2f** in 70:30 ratio respectively (Figure 1). In all cases, the new signal was shifted to lower wavenumber by 50-60 cm^{-1} but still in a range compatible with strained exocyclic double bonds.[18] These FT-IR experiments provided two important pieces of information. Firstly, that the lithiation does not require long reaction times, being complete in just 30 min. Secondly, that the solvent seems to affect the stereoselectivity of the process. In particular, lower levels of stereoselectivity were obtained with the use of a less polar solvent such as toluene in the trapping of (*S*)-**1c-Li**.

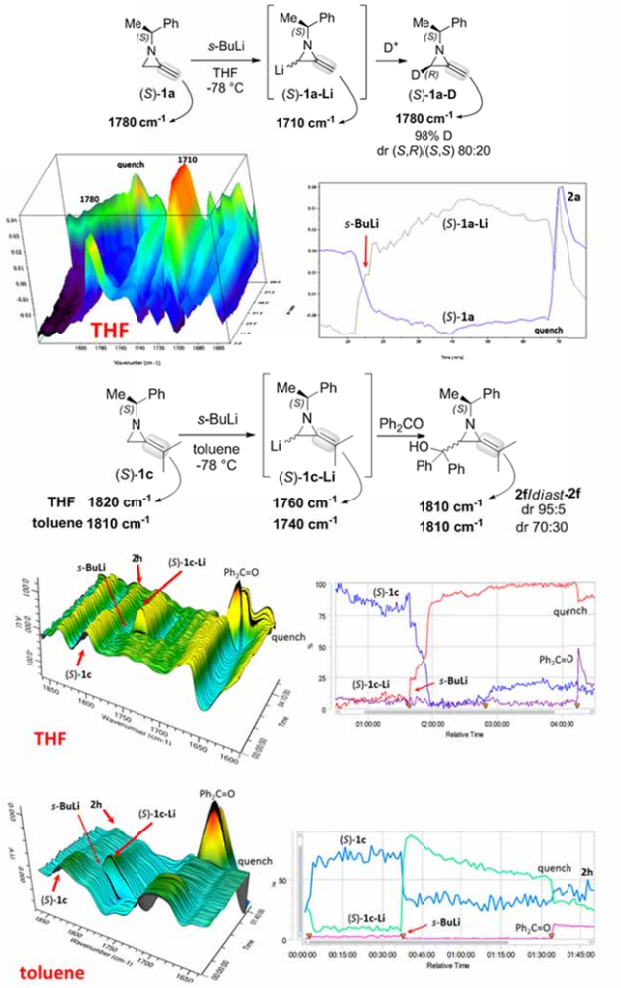
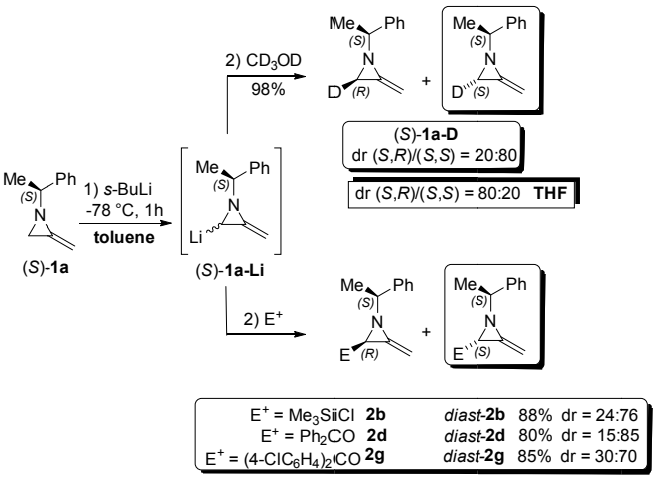


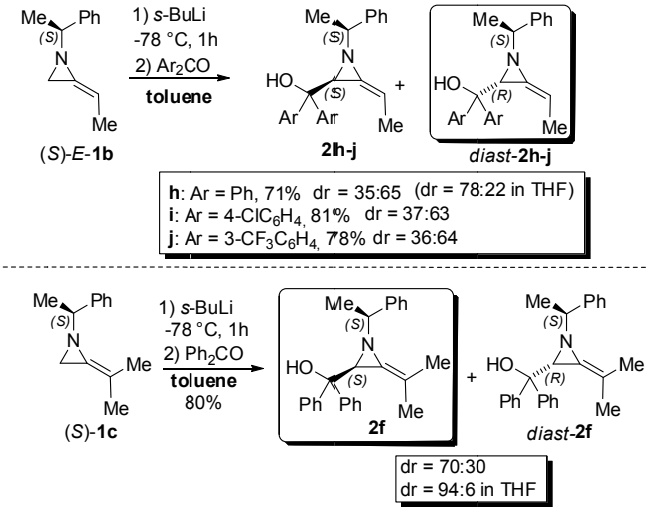
Figure 1. *In situ* monitoring of the lithiation process by FT-IR.

To explore these observations, (*S*)-**1a**, (*S*)-*E*-**1b** and (*S*)-**1c** were lithiated in toluene and quenched with a range of electrophiles. Solvent-dependent stereoselectivity was observed in the lithiation/substition reactions of (*S*)-**1a** (Scheme 3). Trapping of lithiated aziridine (*S*)-**1a** with CD_3OD led to deuterated aziridine (*S*)-**1a-D** in 80:20 diastereomeric ratio. ^{1}H NMR analysis of (*S*)-**1a-D** confirmed the opposite stereochemical preference in this substitution reaction with respect to that run in THF (see supporting information).[13] Similarly, trapping of (*S*)-**1a-Li**, generated in toluene, with benzophenone, Me_3SiCl and 4,4'dichlorobenzophenone furnished adducts **2b**,**d**,**g** and *diast*-**2b**,**d**,**g**. In each case, the major diastereomer observed in toluene had opposite stereochemistry with respect to that obtained in THF (*cf* Table 1, entry 6 and Table 2, entry 7). These data suggest that this solvent-induced reversal in stereoselectivity is independent of the nature of the electrophile and arises in the lithiation step.[19]



Scheme 3. Solvent-dependent stereoselectivity in the lithiation/trapping of methyleneaziridine (*S*)-**1a**.

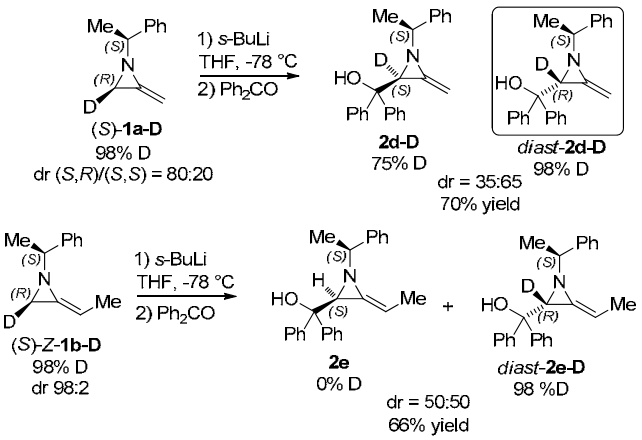
The trapping of lithiated (*S*)-*E*-**1b** with diaryl ketones furnished, in toluene, a mixture of diastereomeric aziridines **2h-j** and *diast*-**2h-j** in moderate diastereomeric ratios but again with opposite stereoselectivity with respect to the THF conditions (Scheme 4).[10] Beside the lower levels of stereoselectivity observed in the reactions of (*S*)-*E*-**1b**, in comparison to (*S*)-**1a**, the solvent effect is remarkable with *diast*-**2h-j** being favored. The stereochemical course for the lithiation/trapping sequence of (*S*)-**1c** in toluene is also reported in Scheme 4. In this case, the same diastereomer **2f** was obtained in both THF and toluene. However, consistent with our other observations, the amount of *diast*-**2f** increased in toluene.



Scheme 4. . Solvent-dependent stereoselectivity in the lithiation/trapping of alkylideneaziridines

In order to rationalize the observed stereoselectivity, we turned our attention to the configurational stability of the lithiated intermediates. In fact, it is reasonable to assume that the presence of two diastereomeric adducts could be the result of a configurational instability of the lithiated intermediates. Based on some previous evidence on the regioselective lithiation of *N*-alkyl-2,3-diphenylaziridines,[20, 21] we decided to exploit the kinetic isotope effect (KIE) to assess the configurational stability of lithiated alkylideneaziridines.[22] We reasoned that, in the presence of an appreciable KIE (that is different rates in proton and deuterium abstraction), the preferential removal of the residual proton would lead to lithiated intermediates having the opposite stereochemistry with respect to those generated from the fully protonated parent aziridines **1a-c** (that are **1a-c-Li** in Scheme 2). Upon

reaction with the electrophile, two situations could be envisaged: a) if the lithiated intermediates equilibrate, the diastereomeric ratios in the adducts should be similar to those observed in the lithiation/trapping of fully protonated parent aziridines; b) conversely, in case of a configurational stability of the lithiated intermediates, upon trapping with the electrophile, a different (if not opposite) diastereomeric ratio should be observed for the adducts. Moreover, in both cases an appreciable degree of deuteration is expected in the final products. Thus, simply evaluating the diastereomeric ratios resulting from the lithiation/trapping of deuterated aziridines, evidence on the configurational stability or instability of the lithiated intermediates would be provided. In order to test this hypothesis, we selected deuterated aziridines that furnished different but appreciable degree of stereoselectivity in the lithiation/trapping sequence, namely aziridine (*S*)-**1a-D** and (*S*)-*Z*-**1b-D**. When deuterated aziridine (*S*)-**1a-D** (dr 80:20, 98% D) was subjected to lithiation with s-BuLi followed by trapping with benzophenone, adducts **2d-D** (75% D) and *diast*-**2d-D** (98% D) were formed in 35/65 ratio respectively (Scheme 5). Applying the same protocol to aziridine (*S*)-*Z*-**1b-D** (dr 98:2, 98% D), a 1:1 diastereomeric mixture of **2e** (0% D) and *diast*-**2e-D** (98% D) was obtained. In both cases, the diastereomeric ratios differ from that resulting from lithiation/trapping of parent aziridine (*S*)-**1a** (dr 80:20) and (*S*)-*Z*-**1b** (dr 93:7). In addition, in the reaction of (*S*)-**1a-D** opposite stereoselectivity was observed, with *diast*-**2d-D** being the major adduct, whilst in the reaction of (*S*)-*Z*-**1b-D** the adduct **2e** was completely non-deuterated. Such results indicate a significant KIE effect in these deprotonations and configurational stability of the lithiated intermediates.



Scheme 5. Experiments proving the configurational stability of lithiated alkylideneaziridines.

At this point, further questions arise: a) how could the solvent induce the stereoselectivity–switch? b) why this stereoselectivity–switch was not observed in the lithiation trapping of (*S*)-**1c** (Scheme 4)? A possible explanation for the above results, could be given if we take into consideration the aziridine nitrogen stereodynamics, complexation and proximity effects. In fact, in the case of *N*-alkyl-2-arylaziridines, such reasoning allowed for rationalizing the solvent- and temperature-dependent regio and stereoselectivity of the lithiation/trapping sequences.[16, 17] The model depicted in Scheme 6 could apply in the case of 2-alkylideneaziridines in which the aziridine nitrogen undergoes slow pyramidal inversion. As a consequence of this slow motion, the ^{1}H NMR spectra of aziridines (*S*)-**1a-c** showed very broad signals at room temperature (Figure 2). Nevertheless, the ^{1}H NMR spectra acquired at low temperature (200 K), clearly showed the signals for the two slowly equilibrating invertomers (Figure 2).

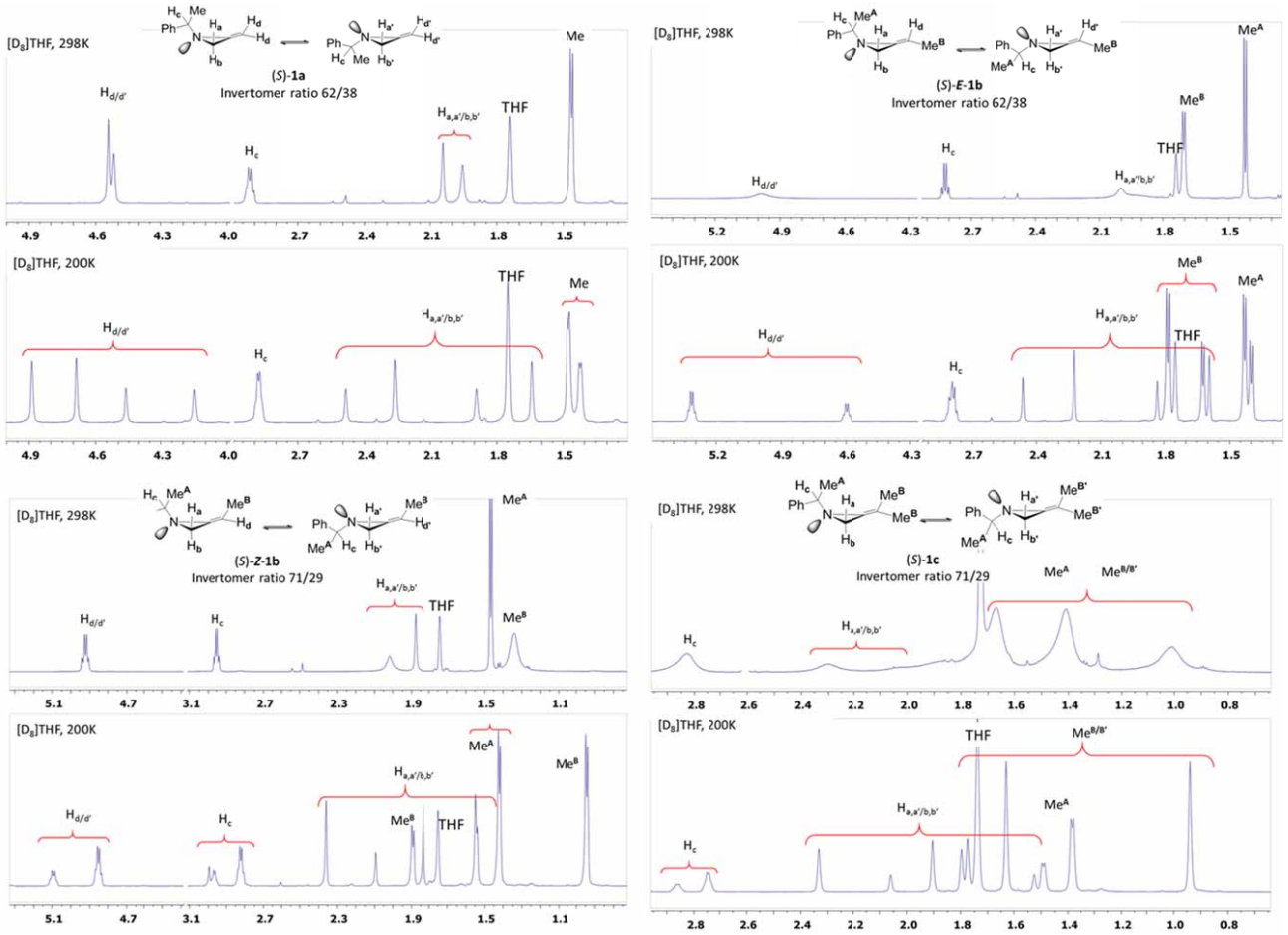
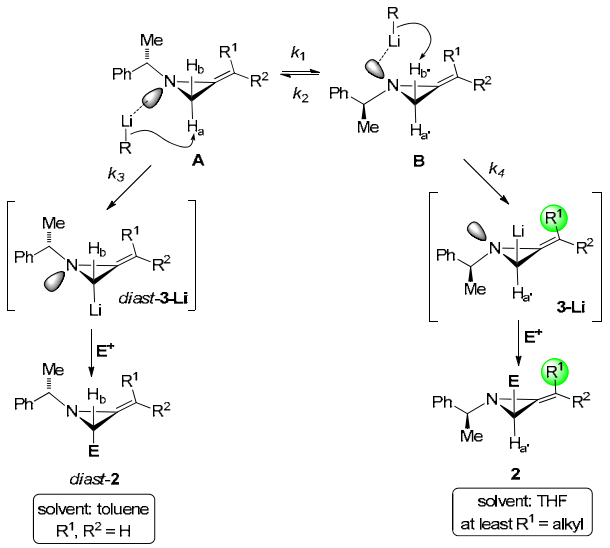


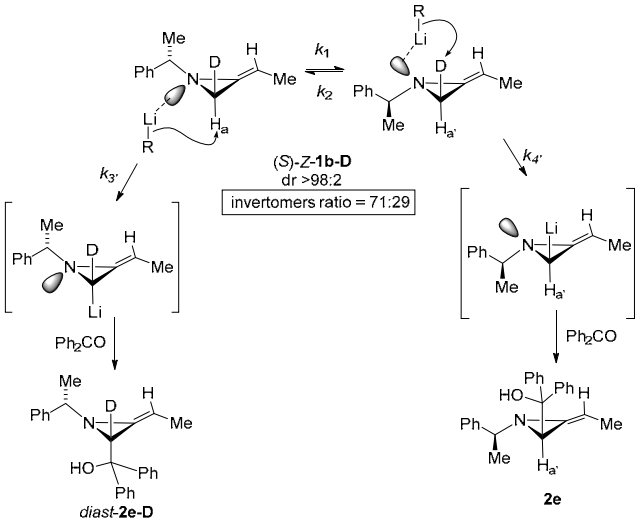
Figure 2. Stereodynamics of alkylideneaziridines by VT NMR under moderate and slow exchange regimes.

Analysis of the low-temperature (200 K) ^{1}H NMR spectra revealed an invertomer ratio of 62:38 for aziridines (*S*)-**1a** and (*S*)-*E*-**1b**, and a 71:29 ratio for aziridines (*S*)-*Z*-**1b** and (*S*)-**1c**. However, even though we were able to reveal the presence of two nitrogen invertomers, it has not proved possible to establish the relative configurations of the major invertomers. Nevertheless, with reference to Scheme 6, for the sake of argument, we assume that a preferential deprotonation *syn* to the nitrogen lone pair of invertomers **A** and **B** would lead to diastereomeric lithiated intermediates **3-Li** and *diast*-**3-Li**. In addition, on the basis of the experiments on deuterated aziridines (Scheme 5), lithiated intermediates **3-Li** and *diast*-**3-Li** should also be configurationally stable, and a retentive electrophilic substitution would furnish adducts **2** and *diast*-**2** respectively. Thus, a possible explanation for the observed stereoselectivity, could rely on a difference between the rates of deprotonation (k_3, k_4 in Scheme 6) with respect to the rates of inversion (k_1, k_2 in Scheme 6). However, regardless of the equilibria involving the lithiating agent, which could have its own aggregation state,[9b] at least three different conditions are foreseen: a) with $k_3 \approx k_4 >> k_1, k_2$ the ratio between **3-Li** and *diast*-**3-Li** would reflect that of the neutral invertomers; b) with $k_1, k_2 >> k_3$ (or k_4) $> k_4$ (or k_3) one prevalent lithiated intermediate should form; c) with k_3 (or k_4) $> k_4$ (or k_3) $\approx k_1, k_2$ a mixture of **3-Li** and *diast*-**3-Li** with an unpredictable ratio is expected. The condition b) could likely explain the high stereoselectivity observed in the lithiation/trapping sequences on aziridines (*S*)-*Z*-**1b** and (S)-**1c** in THF and on (*S*)-**1a** in toluene. On the other hand, conditions a) or c) could apply to (*S*)-**1a**, (*S*)-E-**1b**, in THF where lower level of stereoselectivity resulted.[23]



Scheme 6. Model based on the nitrogen stereodynamics.

Moreover, the model proposed in Scheme 6 could explain the stereoselectivity observed in the lithiation/trapping of deuterated aziridines (*S*)-**1a-D** and (*S*)-*Z*-**1b-D**. In Scheme 7 the model is applied to the lithiation of (*S*)-*Z*-**1b-D** where two invertomers in ca 70:30 ratio are present. In this case, the KIE would make the rates $k_{3'}$ and $k_{4'}$ different enough to allow for a competitive removal of proton H_a; thus the ratio of the lithiated intermediates will vary accordingly leading, upon trapping with benzophenone, to the observed 1:1 diastereomeric mixture of **2e** (0% D) and *diast*-**2e-D** (98% D).



Scheme 7. Nitrogen stereodynamics and KIE.

This model seems to support the idea that nitrogen coordination and proximity effects could be responsible for the highly regio and stereoselective lithiation of 2-alkylideneaziridines.

Conclusions

This study tries to demonstrate the origin of the stereoselectivity in the lithiation/trapping sequence of 2-alkylideneaziridines. New conditions for conducting the lithiation reaction have been discovered by *in situ* FT-IR monitoring. In addition, it has been found that the solvent and the alkene substitution are important factors that lead to a switch in stereoselectivity. Lithiation of fully substituted or Z-configured 2-alkylideneaziridines, such as (*S*)-**1c** or (*S*)-*Z*-**1b**, occurred stereoselectively in THF. In striking contrast, unsubstituted 2-methyleneaziridines, such as (*S*)-**1a**, underwent lithiation with an opposite stereoselectivity in toluene. A model based on complexation and proximity effects has been proposed to rationalize this reactivity. This model assumes that slowly equilibrating N-invertomers undergo deprotonation with different rates and that the stereochemical outcome is established during the deprotonation step. Lithiation experiments on deuterium labeled 2-alkylideneaziridines revealed the configurational stability of the lithiated intermediates. Further stereochemical and spectroscopic studies are underway to support the proposed model, and will be reported in due course.

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† This work is dedicated to Prof. Richard Taylor in the occasion of the 65th birthday.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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