# 2-Lithio-3,3-dimethyl-2-oxazolinyloxirane: Carbanion or Azaenolate? Structure, Configurational Stability, and Stereodynamics in Solution

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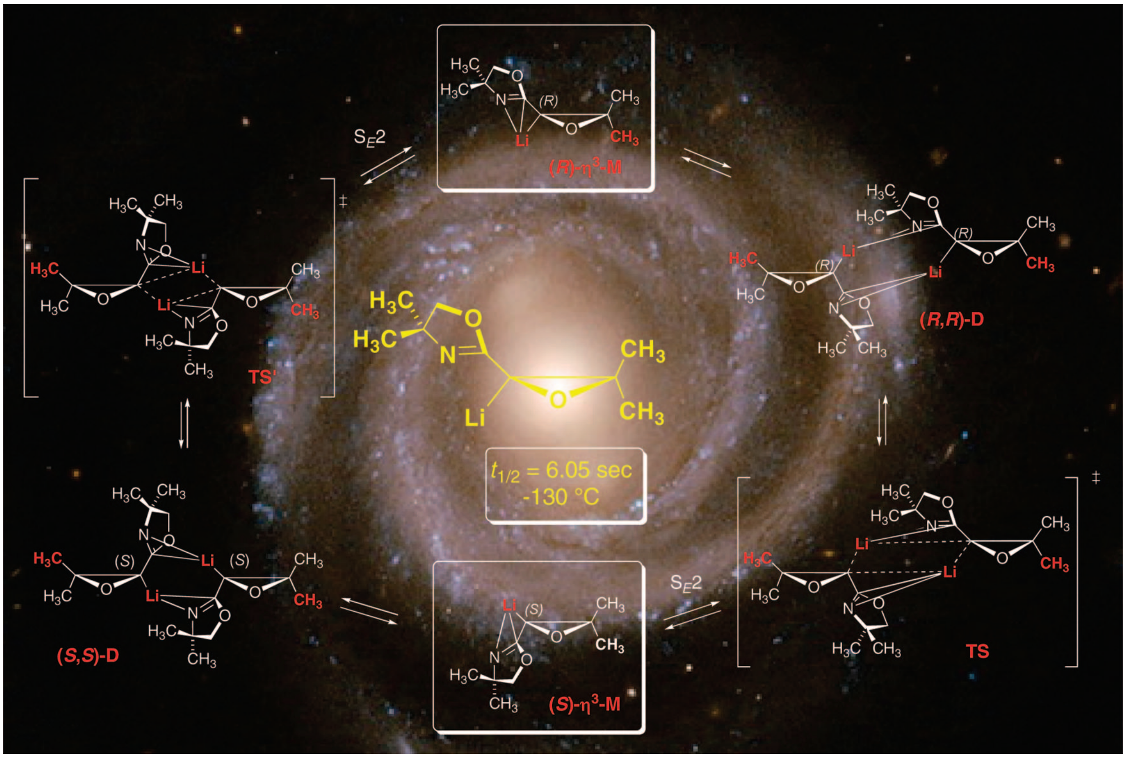

Chemical studies have shown that, in ethereal solvents, oxiranyllithium **Li-1** is configurationally unstable either on the macroscopic (Hoffmann's text) or microscopic time scale at low temperature (175 K). An optically pure sample of oxazolinyloxirane **1**, once deprotonated, racemized within 1 min at −130 °C in THF/$Et_2O$ (3:2) ($t_{1/2}$ = 6.05 s); the application of the Eyring equation suggested a barrier to inversion for **Li-1** of 8.8 kcal/mol at −130 °C. Despite this, **Li-1** exhibited an unusual thermal stability undergoing a successfully deuterium incorporation (>98%) also at 25 °C with a little decomposition. The structure, configurational stability, and stereodynamics in solution of α-lithiated oxazolinyloxirane **Li-1** have been also synergically investigated by means of in situ IR and NMR spectroscopy. IR spectroscopic studies showed that lithiation of **1** is complete at −98 °C within 1 min and is accompanied by a decrease of the C═N wavenumber by only 60 $cm^{-1}$, so supporting the idea that the structure of **Li-1** may be more similar to that of an "organolithium" rather than an "azaenolate". In addition to this, multinuclear magnetic resonance studies suggested that at least in a range of concentration of 0.08−0.3 M, **Li-1** mainly exists in THF as a monomeric $\eta^3$-aza-allyl coordinated species rapidly equilibrating, on the NMR time scale, with a complex mixture of diastereomeric oxazoline-bridged dimeric species variously *intra*aggregated. An exchange mechanism by which monomers would interchange their Li atoms via one of the above dimeric species and which may be responsible for the fast racemization **Li-1** undergoes as soon as is generated has been proposed.

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## Introduction

Oxiranyllithiums are growingly recognized as being extremely versatile synthetic intermediates in organic synthesis, and their reactivity has been widely reviewed and continues to be updated.[1] However, the lack of structural knowledge of these lithiated oxiranes is in sharp contrast to their widespread use. In fact, until recently, just a few computational studies have been published on these intermediates,[2] a few detailed rate studies of LiTMP- and LDA-mediated lithiation of epoxides are available and have been reported by Collum's group,[3] and to the best of our knowledge, only one example of a NMR investigation concerning a α-lithiated triphenylsilyl-substituted oxirane has been mentioned in a thesis dissertation.[4] Moreover, no single-crystal X-ray structures, which might have provided hints at least concerning their static structure, have ever been published,[5] and just an X-ray structure determination concerning a lithiated cyclopropane, such as 1-cyano-2,2-dimethylcyclopropyllithium, which would be the closest compound to a lithiated oxirane, has been reported by Boche.[6] One reason may be that, in many cases, these oxiranyllithiums behave really as "fleeting intermediates" with a lifetime too short to preclude all long-term NMR spectroscopic investigations.[1f] In addition, the well-known carbenoid nature of α-oxygen-substituted organolithium compounds,[7] which manifest with the "spontaneous" tendency they have to give "reductive alkylation" and/or "homocoupling" reactions, needs a careful choice of the experimental conditions, which must be tailored to the properly substituted epoxides under investigation in order to minimize their electrophilic character. In fact, sometimes the best optimized conditions described in the literature to successfully generate these anions and trap them with electrophiles make use of very low temperatures ($\leq -78$ °C) and of nonpolar solvents (such as toluene, hexane);[1h] other times, the employment of polar solvents (such as THF, $Et_2O$) is the winning choice.[1g] The "need" of using ligands (such as TMEDA) to increase the lifetime of these reactive species in solution is also controversial.[1j,8] Generally, placing the anionic center in a small ring or coordinating with lithium gives an inversion rate low enough for the process to be observable by dynamic nuclear magnetic resonance spectroscopy.[9] However, when carbanions are "stabilized" by $\pi$-electron acceptor groups, the stereochemical outcome of their formation and protonation is strongly influenced by the solvent and the cation. For example, the potassium and cesium salts of 7-phenylnorbornyl anion are consistent with a symmetrical planar benzylic carbanion, whereas the same anion with $Li^+$ is pyramidal; the hypothesis drawn by the authors concerning a possible lithium-induced pyramidalization is amazing as well. [10] The first enantioenriched metalated cyclopropyl nitrile possessing macroscopic configurational stability has been also recently described.[11] Our concern in the oxiranyllithium field led us to ascertain that some "stabilized" lithiated oxiranes, such as α-lithiated styrene oxides[12,1g] and α-lithiated oxazolinyloxiranes,[2b,13] do exhibit a singular "carbanionic/carbenoid switch" and a different thermal and configurational stability according to the oxiranyl skeleton, the employed experimental conditions, and the nature of the electrophile they react with.[12c] α-Lithiated oxazolinyloxiranes, which react smoothly with many electrophiles, are known to be "configurationally unstable" on the macroscopic time scale at low temperature.[2b,13a,b] In this paper, we wish to report the results of a combination of a multinuclear magnetic resonance study with an in situ IR investigation to elucidate the nature, the structure, and the stereodynamics, as well as the reasons affecting the configurational instability, of an α-lithiated oxazolinyloxirane such as **Li-1** employed as a model system (Scheme 1).

## Results and Discussion

**Chemical Studies.** Lithiated oxazolinyloxirane **Li-1** could be successfully generated by treating **1** with 1.2 equiv of *s*-BuLi in a donor solvent, such as THF, at −78 °C in the presence or absence of TMEDA (Scheme 1). At this temperature, oxiranyllithium **Li-1** proved to be thermally stable over a period of several hours; indeed, it could be quenched with $CH_3OD$ as **1-D**, almost quantitatively and without decomposition, even after 3 h (95% D, >98% yield).[14] The thermal stability of **Li-1** slowly decreased with time upon warming up the reaction mixture in THF to room temperature, the ketone **3** being the only product deriving from a sort of isomerization reaction probably involving

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[1] (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303–3325. (b) Mori, Y. *Rev. Heteroatom. Chem.* **1997**, *17*, 183–211. (c) Hodgson, D. M.; Gras, E. *Synthesis* **2002**, *12*, 1625–1642. (d) For a special issue on oxiranyl and aziridinyl anions, see: Florio, S. *Tetrahedron* **2003**, *59*, 9693–9684. (e) Hodgson, D. M.; Gras, E. In *Topics in Organometallic Chemistry*; Hodgson, D. M., Ed.; Springer: Berlin, 2003, p 217. (f) Chemla, F.; Vranchen, E. In *The Chemistry of Organolithium Compounds*; Rappoport, Z., Marek, I., Eds.; John Wiley & Sons: New York, 2004; Vol. 2, Chapter 18, p 1165. (g) For a recent account on α-lithiated aryloxiranes, see: Capriati, V.; Florio, S.; Luisi, R. *Synlett* **2005**, *9*, 1359–1369. (h) Hodgson, D. M.; Bray, C. D. In *Aziridine and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH Verlag GmbH & Co. KgaA: Weinheim, 2006; Chapter 5, p 145. (i) Padwa, A.; Murphree, S. *ARKIVOC* **2006**, (iii), 6–33. (j) For a recent review on α-lithiated-α-substituted oxiranes, see: Capriati, V.; Florio, S.; Luisi, R. *Chem. Rev.* **2008**, *108*, 1918–1942.

[2] (a) Boche, G.; Bosold, F. B.; Lohrenz, J. C. W.; Opel, A.; Zulauf, P. *Chem. Ber.* **1993**, *126*, 1873–1885. (b) Abbotto, A.; Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Pierrot, M.; Salomone, A. *J. Org. Chem.* **2001**, *66*, 3049–3058. (c) Pratt, L. M.; Ramachandran, B. *J. Org. Chem.* **2005**, *70*, 7238–7242.

[3] (a) Wiedemann, S. H.; Ramírez, A.; Collum, D. B. *J. Am. Chem. Soc.* **2003**, *125*, 15893–15901. (b) Ma, Y.; Collum, D. B. *J. Am. Chem. Soc.* **2007**, *129*, 14818–14825.

[4] Opel, A. Dissertation, Universität Marburg, 1993.

[5] Only the isolation and crystal structure of a presumed intermediate formed in the reaction of an organolithium compound with an epoxide has been reported until to date: Harder, S.; Boersma, J.; Brandsma, L.; Kanters, J. A.; Duisenberg, J. M.; van Lenthe, J. H. *Organometallics* **1990**, *9*, 511–516.

[6] The tetrahedral configuration of the anionic carbon atom seen in the solid state for the α-cyanocyclopropyl anion resulted to be in agreement with calculations and also nicely confirmed the results of H/D exchange experiments performed with cyclopropylnitriles in solution: Boche, G.; Harms, K.; Marsch, M. *J. Am. Chem. Soc.* **1988**, *110*, 6925–6926.

[7] Boche, G.; Lohrenz, J. C. W. *Chem. Rev.* **2001**, *101*, 697–756.

[8] For an enlightening account about the role TMEDA may have in organolithium chemistry, see: Collum, D. *Acc. Chem. Res.* **1992**, *25*, 448–454.

[9] For the structure and dynamics of 1-lithio-1-phenylcyclopropanes, see: Hoell, D.; Schnieders, C.; Müllen, K. *Angew. Chem., Int. Ed.* **1983**, *22*, 243–244.

[10] People, P. R.; Grutzner, J. B. *J. Am. Chem. Soc.* **1980**, *102*, 4709–4715.

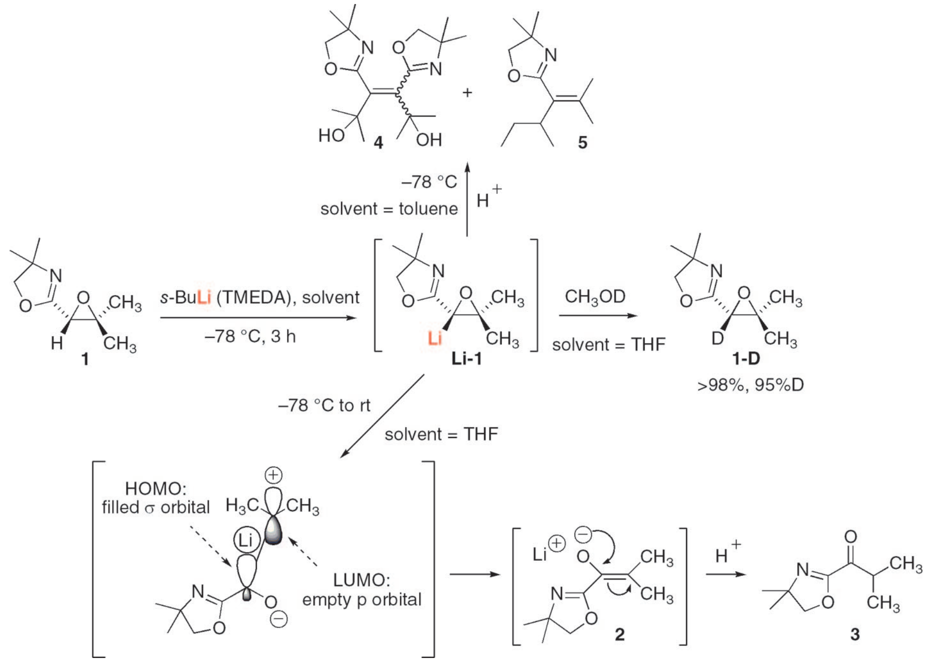
[11] Carlier, P. R.; Zhang, Y. *Org. Lett.* **2007**, *9*, 1319–1322.

[12] (a) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A. *Org. Lett.* **2002**, *4*, 2445–2448. (b) Capriati, V.; Florio, S.; Luisi, R.; Nuzzo, I. *J. Org. Chem.* **2004**, *69*, 3330–3335. (c) Capriati, V.; Florio, S.; Luisi, R.; Perna, F. M.; Barluenga, J. *J. Org. Chem.* **2005**, *70*, 5852–5858. (d) Capriati, V.; Florio, S.; Luisi, R.; Salomone, A.; Cuocci, C. *Org. Lett.* **2006**, *8*, 3923–3926. (e) Capriati, V.; Degennaro, L.; Florio, S.; Luisi, R.; Punzi, P. *Org. Lett.* **2006**, *8*, 4803–4806.

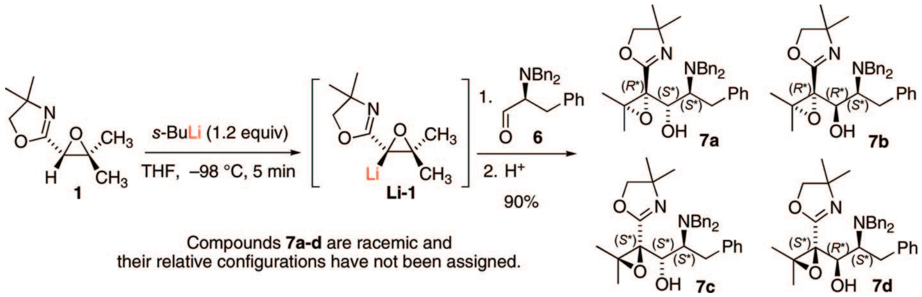
[13] (a) Luisi, R.; Capriati, V.; Carlucci, C.; Degennaro, L.; Florio, S. *Tetrahedron* **2003**, *59*, 9707–9712. (b) Luisi, R.; Capriati, V.; Degennaro, L.; Florio, S. *Org. Lett.* **2003**, *5*, 2723–2726. (c) Florio, S.; Perna, F. M.; Luisi, R.; Barluenga, J.; Fañanás, F. J.; Rodríguez, F. *J. Org. Chem.* **2004**, *69*, 9204–9207.

[14] In the lithiation of oxazolinyloxirane **1**, TMEDA does not seem to play a crucial role in accelerating oxiranyllithium reaction rate as well as in improving product yields. Indeed, as has been pointed out by Collum,[8] "TMEDA appears to manifest a highly substrate dependent affinity for lithium", and in the case of **1**, the results obtained from the described chemical studies in the presence or absence of TMEDA were the same.

**SCHEME 1**



**SCHEME 2**



Compounds **7a-d** are racemic and their relative configurations have not been assigned.

the enolate **2** (Scheme 1).[15] An $E_1$-like mechanism involving the unusual $C_\beta$-O bond cleavage (with respect to the oxazoline moiety)[16] in the rate-determining step, which would permit the ideal alignment of the orbitals to be involved in the C−C double bond formation of the enolate, may be operating. However, the electrocyclic α-ring-opening mechanism, which has been claimed by several authors[1f] in the case of other oxiranyllithiums, cannot be ruled out, at least at present. It is worth noting that, upon warming the reaction mixture containing the oxiranyllithium **Li-1** to room temperature, the above isomerization reaction takes place very slowly; indeed, we succeeded in trapping **Li-1** with $CH_3OD$ also at 25 °C in 85% yield (>98% D) and 65% yield (>98% D) starting from 0 (50 min as the reaction time) and −78 °C (6 h as the whole reaction time), respectively. To the best of our knowledge, this should be the first example of an oxiranyllithium showing such an unusual thermal stability.[17] It might be useful to point out that oxiranyllithium **Li-1** exhibited a carbene-like reactivity mainly in a nonpolar solvent. In fact, running the deprotonation of **1** in toluene, the carbenoid character of **Li-1** became favored with time, also at −78 °C, and the formation of diastereomeric enediols **4** and alkene **5** (particularly using excess *s*-BuLi),[18] as the result of a "homocoupling"[19a] and a "reductive alkylation" reaction,[19b,c] respectively, competes strongly.

**Configurational Stability: Hoffmann's Test and Estimation of the Racemization Rate.** Information about the configurational stability of a chiral organolithium, on the time scale of its addition to an electrophile, can be gathered, in principle, by the Hoffmann test,[20] which is based on kinetic resolution. To this end, first, racemic oxiranyllithium **Li-1** was allowed to react at −98 °C with the racemate of *N*,*N*-dibenzylphenylalaninal **6**[21] (Scheme 2), which generally shows good reactivity toward a wide range of organolithium reagents. In most cases, starting from a racemic mixture of the chiral organolithium, the

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(15) For an oxiranyllithium-based synthesis of α-keto-2-oxazolines, see: Capriati, V.; Florio, S.; Luisi, R.; Russo, V.; Salomone, A. *Tetrahedron Lett.* **2000**, *41*, 8835–8838.

(16) For other examples of $C_\beta$-O bond cleavage in metalated oxiranes, see: Kasatkin, A.; Whitby, R. J. *Tetrahedron* **2003**, *59*, 9857–9864.

(17) Generally, the presence of an electron-withdrawing group on the lithiated carbon is able to increase the anion lifetime (ref 1j). However, the factors responsible for tuning the reactivity of an oxiranyllithium towards a carbanion or a carbene-type behaviour are still an open question.

(18) Performing the lithiation of **1** in toluene in the presence of an excess *s*-BuLi, oxiranyllithium **Li-1** completely converted into an equimolar mixture of diastereomeric enediols **5** (dr 1:1) and alkene **6** (both not isolated), which were the only two products that could be checked in the crude by $^1$H and $^{13}$C NMR and GC-MS.

(19) (a) Lohse, P.; Loner, H.; Acklin, P.; Sternfeld, F.; Pfaltz, A. *Tetrahedron Lett.* **1991**, *32*, 615–618. (b) Doris, E.; Dechoux, L.; Mioskowski, C. *Tetrahedron Lett.* **1994**, *35*, 7943. (c) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337.

(20) (a) Hirsch, R.; Hoffmann, R. W. *Chem. Ber.* **1992**, *125*, 975–982. (b) Hoffmann, R. W.; Julius, M.; Ruhland, T.; Frenzen, G. *Tetrahedron* **1994**, *50*, 6049–6060.

(21) Reetz, T. M.; Drewes, M. W.; Schwickardi, R. *Org. Synth.* **1999**, *76*, 110–116.

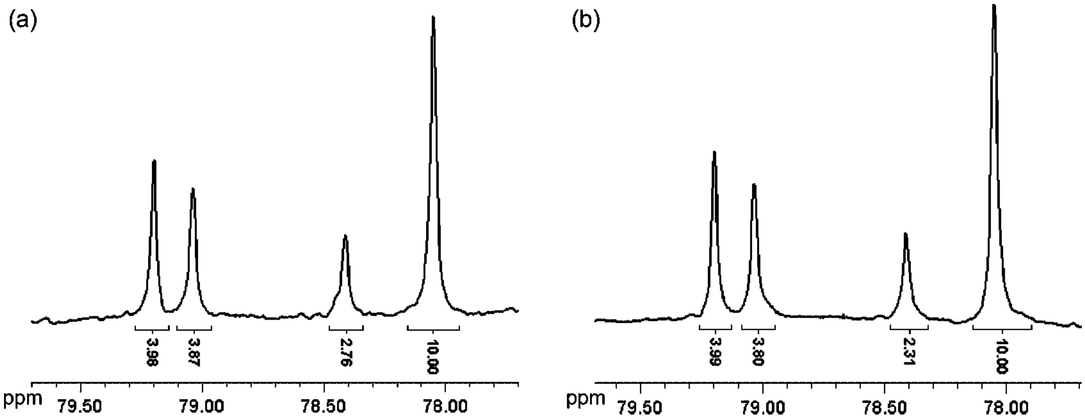


**FIGURE 1.** First (a) and second experiment (b): integration of $^{13}$C NMR signals, relative to the oxazoline methylenic carbons, each peak being representative of a single diastereomer.

asymmetric induction from the resident chirality center in **6** is high enough to favor the formation of only two adducts. Unfortunately, in the case of oxiranyllithium **Li-1**, the asymmetric induction was poor, and a mixture of the four possible adducts **7a**−**d** formed (Scheme 2, 90% overall yield). The diastereomeric ratio was accurately determined from $^{13}$C NMR spectrum on the crude reaction mixture to be 49:19:19:13 (Figure 1a). Since none of the pairwise combinations of these numbers may lead to 50:50, kinetic resolution would be at least 1.6:1. For this reason, there is no need to assign the relative stereochemistry to the individual diastereomers. Separation of the four diastereomeric adducts **7a**−**d** by column chromatography (see Experimental Section) confirmed their structural assignment. In a second experiment, the racemic oxiranyllithium **Li-1** was allowed to react with the enantiomerically pure aldehyde **6**. The ratio of diastereomers, again determined by $^{13}$C NMR spectrum of the crude reaction mixture, was 50:20:19:11 (Figure 1b). The almost identical diastereomeric ratio at conversions of >50% in the two experiments would indicate configurational lability of oxiranyllithium **Li-1** on the time scale set by the rate of its addition to the aldehyde, that is, within 5 min at temperatures as low as −100 °C. In other words, racemization of oxiranyllithium **Li-1**, under the above conditions, occurs faster than its addition to the electrophile.

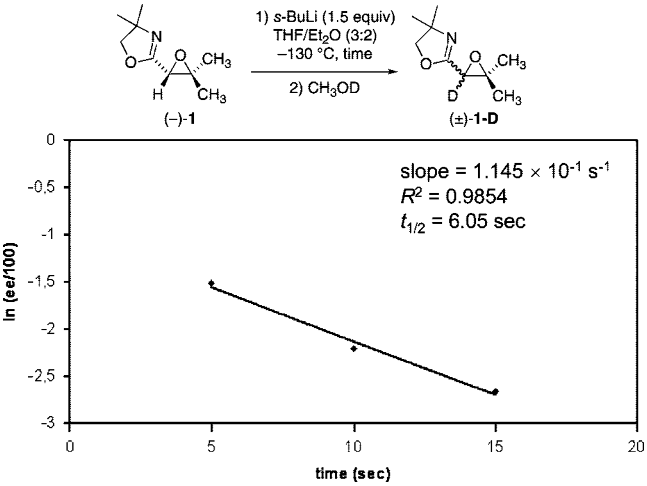
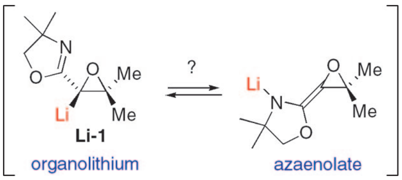


**FIGURE 2.** Estimation of the racemization half-life of the oxiranyllithium **Li-1** derived from (−)-**1**.

**SCHEME 3**



With the aim of calculating the rate of racemization of **Li-1** at a certain temperature, a chromatographic separation of a racemic mixture of **1** was preliminary set up on an analytical chiral stationary HPLC phase and successfully carried out on the same preparative chiral stationary HPLC phase (see Experimental Section); the individual enantiomers were each obtained with ee ≥ 99.5%. A deprotonation (1.2 equiv *s*-BuLi)/deuteration ($CH_3OD$) experiment performed on (−)-**1**[22] in THF at −98 °C showed that just within 10 s the deuteration was almost quantitative (>98% D) but **1-D** was recovered completely racemic. These data are consistent with the idea that oxiranyllithium **Li-1** tends to undergo a very quick racemization soon after its generation, under the above conditions, and is configurationally unstable also on the microscopic time scale at −98 °C. However, when the deprotonation was carried out with 1.5 equiv of *s*-BuLi at −130 °C using a mixture of 3:2 THF/$Et_2O$ as the solvent system (liquid $N_2$−THF/$Et_2O$ 3:2 being the cooling bath) followed by a $CH_3OD$ quench, **1-D** was recovered with 22% ee (84% D), 11% ee (85% D), and 7% ee (95% D) after a 5, 10, and 15 s deprotonation time, respectively (Figure 2). By plotting ln(ee/100) vs time, it was possible to estimate the rate of racemization[23] (Figure 2). This plot showed a roughly good linear relationship ($R^2 = 0.9854$), and the slope, corresponding to $-k_{\rm rac}$, indicates an estimated racemization $t_{1/2}$ of 6.05 s at −130 °C. Application of the Eyring equation[24] to the estimated $k_{\rm rac}$ for the oxiranyllithium **Li-1** derived from (−)-**1** indicates a barrier to inversion ($\Delta G^{\ddagger}_{\rm rac}$) of 8.8 kcal/mol at −130 °C in THF/$Et_2O$ (3:2).

The structure and the stereodynamics of oxiranyllithium **Li-1** in solution were synergically investigated by means of IR and NMR spectroscopic measurements.

**IR Spectroscopic Studies.** A first key feature about the structure of an oxiranyllithium such as **Li-1** that needs to be

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[22] The absolute configuration to enantiomers (−)- and (+)-**1** could not be assigned to date.

[23] Kawabata, T.; Suzuki, H.; Nagae, Y.; Fuji, K. *Angew. Chem., Int. Ed.* **2000**, *39*, 2155–2157. See also ref11.

[24] Activation free energy is calculated as $\Delta G^{\ddagger}_{\rm rac} = 4.576T[10.319 + \log(t/k_{\rm rac})]$: Eyring; H., *Chem. Rev.* **1935**, *17*, 65–77.

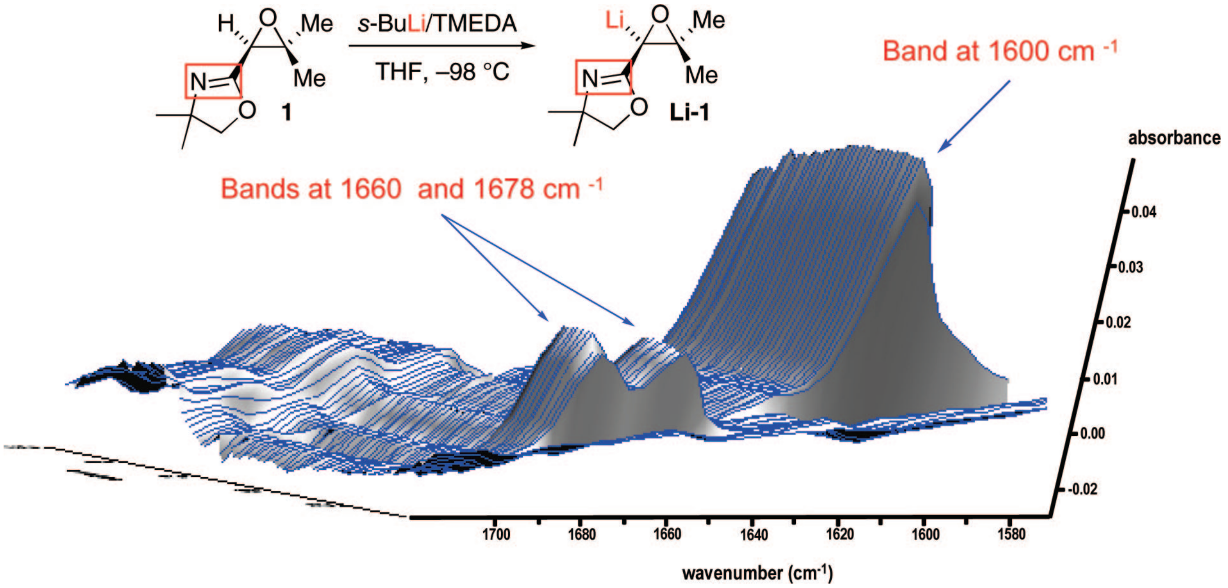

**FIGURE 3.** Progression of the reaction between oxazolinyloxirane **1** and 1 equiv of *s*-BuLi in the presence of 1 equiv of TMEDA monitored by ReactIR. Spectra displayed in 3D view: overlapped regions 1600−1700 cm$^{-1}$.

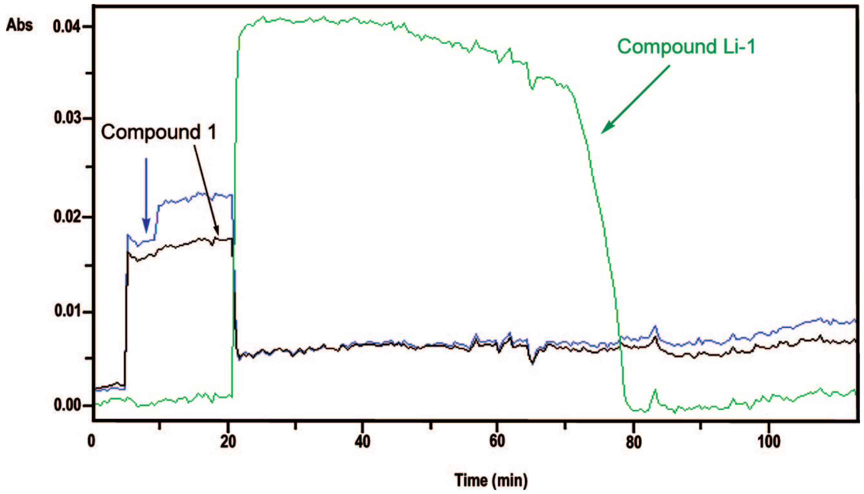

**FIGURE 4.** Reaction profile of the lithiation of **1** to give **Li-1** obtained by plotting the intensities of the iminic absorbance at 1660, 1678, and 1600 cm$^{-1}$ against the time.

answered is the following: Is **Li-1** in solution an azaenolate or a true organolithium (Scheme 3)?

We decided to use in situ IR spectroscopy to obtain hints about the force constant of the oxazoline iminic moiety adjacent to the oxiranyl carbanion. The spectra were recorded with a ReactIR 4000, and the experiments were monitored under inert atmosphere as follows: (1) first the THF was introduced and then the epoxide; (2) 1 equiv of TMEDA was added, and the reaction mixture was cooled to −98 °C; (3) 1.0 equiv of a commercial solution of *s*-BuLi was introduced all at once; (4) the reaction was finally quenched with $CH_3OD$. As it can be noted in Figure 3, the IR spectrum of the starting oxazolinyloxirane **1** displays two bands for the stretching frequency of the oxazoline iminic group at 1660 and 1678 cm$^{-1}$, due to two different conformations of the C=N moiety in solution. This was proved by ab initio geometry optimization of the oxazolinyloxirane **1** at the B3LYP/6-31 G* level of theory, which resulted in two local minimum-energy structures, each characterized by zero imaginary frequencies with a difference of $\Delta\upsilon = 13$ cm$^{-1}$ for the two stretching frequencies of the oxazoline iminic group relative to the two equilibrium geometries and a $\Delta E = 0.25$ kcal/mol (see Supporting Information). Addition of 1 equiv of *s*-BuLi after 21 min resulted in a prompt and complete disappearance of the above bands (within 1 min in THF and in the presence of TMEDA; see Figure 4), whereas a new absorption emerged at 1600 cm$^{-1}$, which was assigned to the lithiated species **Li-1** (Figures 3 and 4). The fact that this new stretching frequency of the iminic group was shifted by only 60 cm$^{-1}$ to lower wavenumbers is indicative of a weakening of the C=N bond probably caused by intramolecular coordination of the iminic nitrogen to lithium. A shift to lower wavenumbers of 34 cm$^{-1}$ and a stretching frequency of 1607.9 cm$^{-1}$ has been also reported by Meyers et al.[25] for formamidines upon α-lithiation as a consequence of a strong complexation of the iminic nitrogen with lithium. On the other hand, in the case of alkylidene epoxides (such as 1-*tert*-butylallene oxide), a stretch-

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(25) Meyers, A. I.; Rieker, W. F.; Fuentes, L. M. *J. Am. Chem. Soc.* **1983**, *105*, 2082–2083.

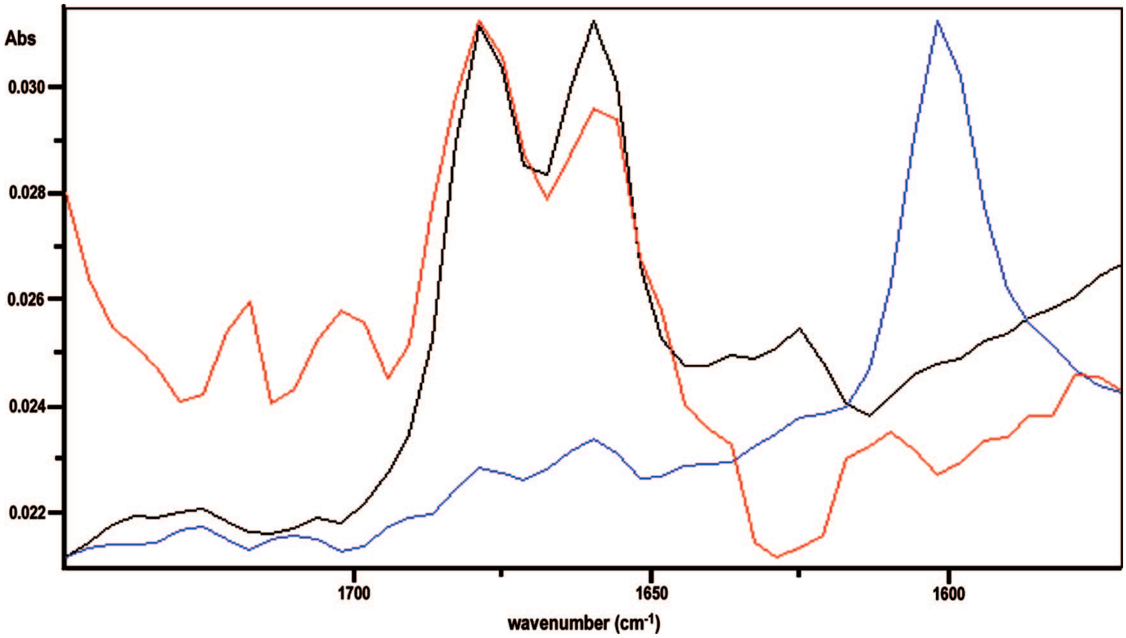

**FIGURE 5.** Progression of the lithiation reaction versus absorbance in 2D. Black: starting oxazoliniloxirane **1**. Blue: after addition of *s*-BuLi. Red: after quenching and warming up.

ing frequency of 1780 cm$^{-1}$ was recorded instead.[26] On the basis of the above results, it is reasonable to assume, in the first place, that imine chelation in **Li-1**, in solution, may be more favored than ether chelation[27] and that the structure of **Li-1** should be more similar to that of an oxiranyllithium rather than an azaenolate. After 84 acquisitions (almost 80 min), the reaction mixture was quenched with an excess $CH_3OD$, the cooling bath was taken away, and the system warmed to room temperature. The IR spectrum showed a disappearance of the 1600 cm$^{-1}$ band, whereas the original 1660 and 1678 cm$^{-1}$ bands came back to a certain amount (Figure 5). The oxazolinyloxirane **1** was quantitatively recovered and was 98% D. Now, the question is which type of intramolecular coordination may be favored. Can the in-plane lone pair on oxazoline nitrogen efficiently coordinate lithium? Which should be the preferred aggregation state of **Li-1** in solution, and in which way such a "configurational instability" may be rationalized? To answer these questions, a multinuclear magnetic resonance investigation was performed.

**NMR Spectroscopic Studies: $^{13}$C and $^{7}$Li NMR Investigation of 0.2 M Li-1 in THF-*d*$_8$ at 170 K.** As a first step, in two separate runs, a 0.2 M sample of **1** was treated with 0.8 and 2.0 equiv of a commercial solution of cyclohexane-free *s*-BuLi in THF-*d*$_8$ at 170 K. The two resulting $^{13}$C NMR spectra were identical (apart from additional signals deriving from excess of **1** or excess organolithium), indicating that no mixed aggregates between **Li-1** and excess *s*-BuLi formed. Therefore, these spectra have to be ascribed only to the oxiranyllithium **Li-1** either because several preparations were fully reproducible or because a spectroscopic analysis ($^{1}$H, $^{13}$C NMR) of the hydrolysis products of **Li-1** (once quenched with $CH_3OD$) showed the exclusive presence of **1-D**, so ruling out the presence of products deriving from side reaction of the oxiranyl anion. Running a $^{13}$C NMR spectrum of **Li-1** (0.2 M, 1 equiv *s*-BuLi) at natural abundance at 170 K, all signals were very broad, and apparently at least three sets of signals (one being stronger than the other two) were detected for some carbon atoms, indicative of the presence of more than one species in solution (Figure 6b). The $^{7}$Li NMR spectrum exhibited, within 1 ppm, besides the main signal centered at $\delta$ 0.77, up to eight peaks, all related to nonequivalent lithiums, either as shoulders of the previous one at $\delta$ 0.77 or close to the signals at $\delta$ 0.44 and 0.35 (Figure 6c). This fact supports the hypothesis that several species differently aggregated seem really to coexist at this temperature and concentration in solution (vide infra). Most diagnostic and interesting for the structure and the dynamic behavior of **Li-1** were in particular, in the $^{13}$C NMR spectrum, the shifts and multiplicities of the oxazoline iminic carbon, the oxiranyl carbanion, and the two geminal oxiranyl methyl groups. The C9 oxazoline carbon in **Li-1** consists of three signals in the range 178.0−181.0 ppm (peaks at $\delta$ 180.2, 179.6, 178.7; see numbering in Figure 6), the stronger and the broader one being that falling at 179.6 ppm. This carbon experienced a low-field shift of more than 17 ppm further to lithiation (Figure 6a,b). In the case of *ortho*-lithiated phenyloxazolines, where a chelation between the nitrogen lone pair and the lithium takes place, the iminic carbon was downfield shifted only 10.5 and 11.8 ppm for the monomer and the bridged dimer, respectively.[27] Thus, in our case, the greater downfield shift observed may suggest a strong decrease of the $\pi$-electron density occurring at the C=N bond. One possibility is that lithium occupies a $\eta^3$-aza-allyl position (Figure 6). This interpretation is supported, inter alia, by the nonequivalence of the two oxazoline geminal methyls C3,C4 in lithiated species, as one would be expect for a "locked" geometry such as that. These geminal methyls, likewise to the oxazoline iminic carbon, were downfield shifted showing a complex pattern between 30.0 and 32.0 ppm, whereas in the starting oxazolinyloxirane they were isochronous, falling at 28.7 ppm (Figure 6a). High level ab initio calculations performed at the DFT level on two diastereomeric $\beta$-phenyl-substituted α-lithiated oxazolinyloxiranes[2b] suggested a distorted sp$^3$ arrangement for the lithium cation-bearing carbanionic carbon

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[26] Chan, T. H.; Ong, B. S. *J. Org. Chem.* **1978**, *43*, 2994–3001.

[27] Also in the case of *ortho*-lithiated phenyloxazolines, nitrogen chelation has been reported to be stronger than oxygen chelation; see: Jantzi, K. L.; Guzei, I. A.; Reich, H. J. *Organometallics* **2006**, *70*, 3375–3382.

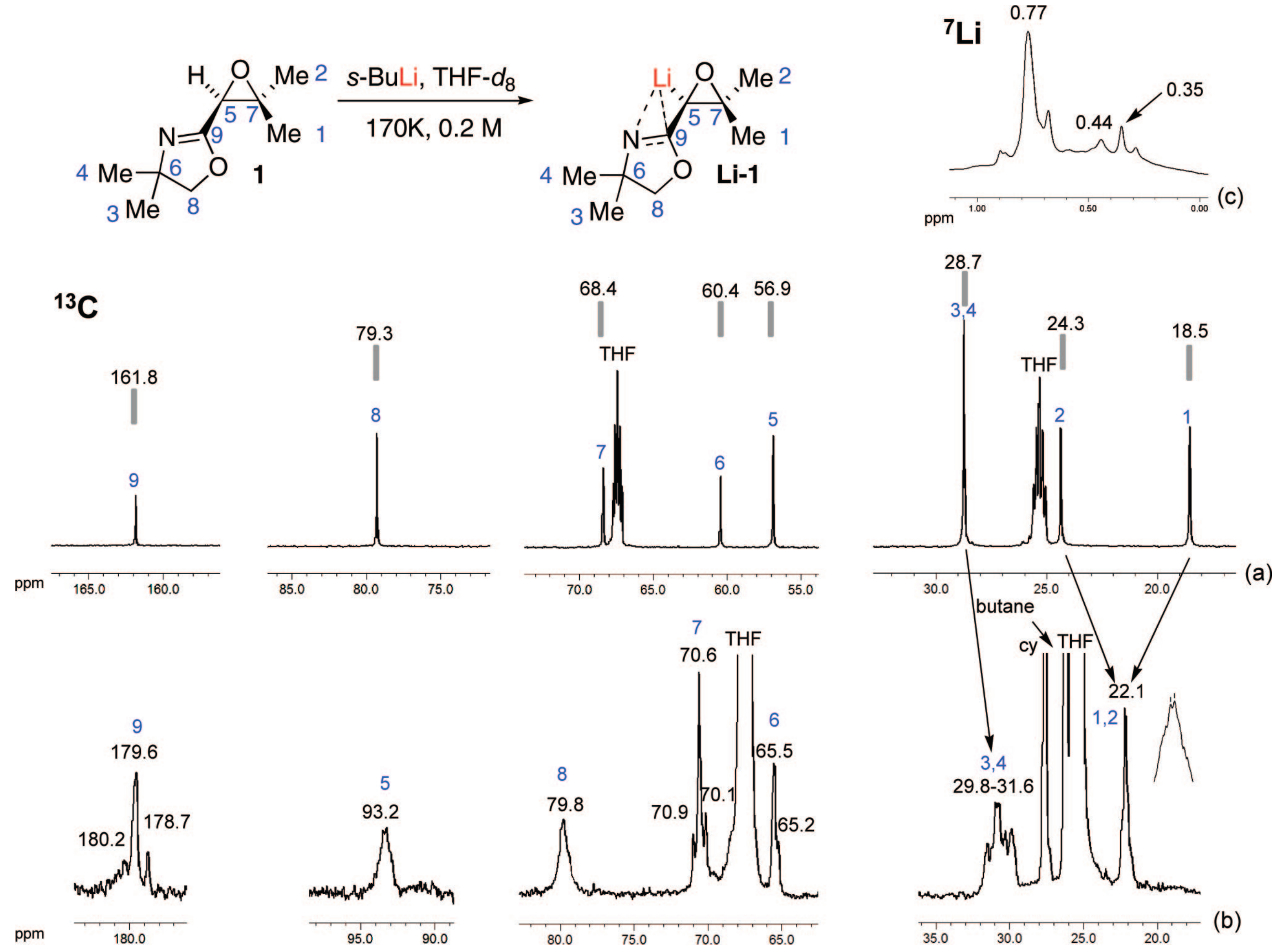

**FIGURE 6.** (a) $^{13}C$ NMR spectrum of 0.2 M **1** in THF-$d_8$ at 170 K. (b) $^{13}C$ NMR spectrum of 0.2 M **Li-1** in THF-$d_8$ at 170 K. (c) $^{7}Li$ NMR spectrum of 0.2 M **Li-1** in THF-$d_8$ at 170 K. All spectra were measured at natural abundance lithium and carbon. Assignments were confirmed by DEPT 135 experiments. Cy represents cyclohexane.

atom, probably in order to allow a stabilizing intramolecular coordination between lithium, the oxazoline nitrogen, and $\pi$-bond, that is, a trihapto $\eta^3$-aza-allyl coordination. The above spectroscopic evidence seem therefore to fit very well computational predictions obtained from similar lithiated systems.

Upon lithiation, the oxiranyl α-carbon (C5) was downfield shifted of about 36.5 ppm, and its signal appeared as a featurless lump not revealing any line splitting due to $^{7}Li$ coupling. This deshielding has not necessarily to be interpreted in terms of a rehybridization of the anionic carbon atom but may be just the consequence of a "carbenoid effect"; in other terms, as pointed out by Boche,[7] "the deshielding of the $^{13}C$ carbenoid atom is not only due to the isotropic chemical shifts $\sigma$ but also due to the dia- or paramagnetic contributions of the various localized molecular orbitals".[28] Being α-lithiated ether "carbenoids", the deshielding of the lithiated $^{13}C$ atoms is an indication of their carbenoid character, that is, of their electrophilic reactivity. In this view, the carbenoid character of α-lithiated oxazolinyloxirane **Li-1** is almost as strong as that of α-lithiated triphenylsililoxirane ($\Delta\delta$ = 36.9).[4,7] Interestingly, the two geminal oxiranyl methyl groups (C1,C2) which were nonequivalent in oxazolinyloxirane **1** (18.5 and 24.3 ppm), merged into a broad peak in lithiated species **Li-1**, exhibiting an average chemical shift value at $\delta$ 22.1 (Figure 6b); it indeed corresponds to two overlapping broad signals at $\delta$ 22.09 and 22.11. This fact may be consistent with a nonprivileged fixation of the lithium on one of the two sides of the plane of the oxirane ring and also suggests either a rapidly inverting tetrahedral or a planar configuration of the corresponding α-lithiated oxiranyllithium, both implicating an enantiomeric conversion; in other words, the oxiranyl α-carbanionic carbon atom behaves as a prochiral entity. On the basis of the above considerations, an inverting tetrahedral configuration may be most probably involved.

**Effect of Temperature.** Cooling down the above 0.2 M sample of **Li-1** to 160 K, near to the freezing point of the THF solution, produces broadening for the various carbon resonances in the corresponding $^{13}C$ NMR spectra, but we were still unable either to decoalesce signals representative of the "individual species" in dynamic equilibrium in solution or to obtain Li−C coupling information that would be indicative for aggregation states of **Li-1** (Figure 7).[29] Similarly, after cooling the sample,

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[28] This is a well-studied effect in PhLi where the unusual downfield shift of the *ipso* carbon is presumably due to the large paramagnetic term, $\sigma_{para}$, of the shielding constant; see: (a) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371–2739. (b) Reich, H. J.; Green, D. P.; Medina, M. A.; Goldenberg, W. S.; Gudmundsson, B. Ö.; Dykstra, R. R.; Phillips, N. H. *J. Am. Chem. Soc.* **1998**, *120*, 7201–7210.

[29] Lowering further the temperature of a 0.2 M sample of **Li-1** to 150 K with a 3:2 THF-$d_8$/Et$_2$O-$d_{10}$ mixture as the solvent system led to a considerable broadening of the $^{13}C$ signals with both a poor resolution and a poor signal-to-noise ratio.

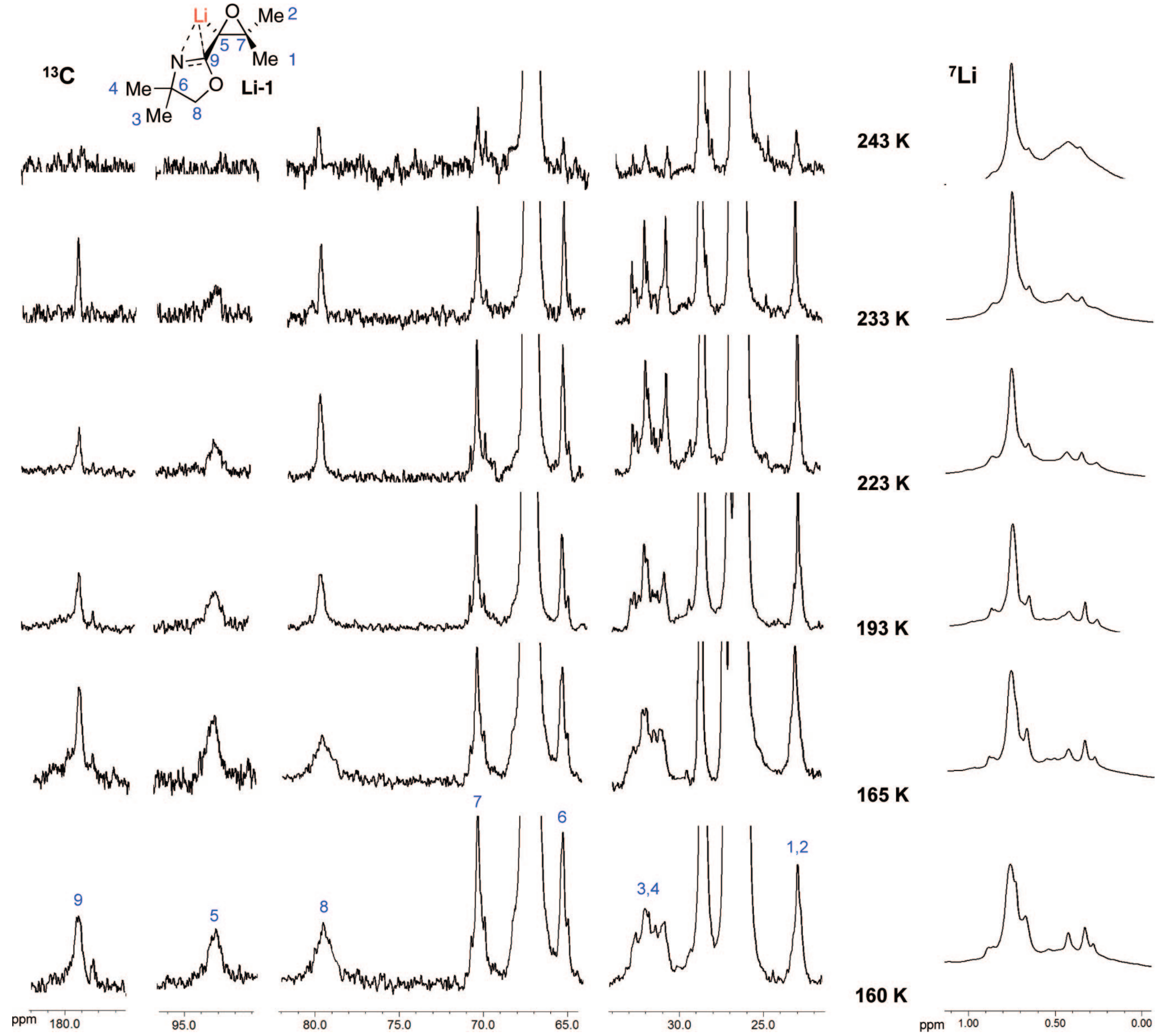

**FIGURE 7.** Variable-temperature $^{13}$C and $^{7}$Li NMR spectra of 0.2 M **Li-1** in THF-$d_8$. All spectra were measured at natural abundance lithium and carbon.

the relatively unresolved $^{7}$Li resonances (Figure 6c) could not be further split, and particularly in the range of 0.60−0.90 ppm, signals continued to be strongly overlapped. On the contrary, when the sample is warmed to 243 K (Figure 7), signals of the various carbons sharpen and $^{7}$Li NMR resonances tend to undergo coalescence. Also in consideration of the fact that chemical studies suggested a barrier to racemization of just 8.8 kcal/mol at −130 °C for **Li-1**, we interpret the above data in terms of possible *inter/intra*aggregate exchanges occurring still fast on the $^{13}$C NMR time scale even at a temperature as low as 150 K.[29] Above 233 K, the $^{13}$C NMR signals of both carbanionic and iminic carbons are almost coalesced most probably because a faster *inter*aggregate exchange is now under way. To get more insights about the nature of the above aggregation states, we found it instructive to perform a variable concentration study.

**Variable-Concentration Study.** A 0.3 M sample of **Li-1** in THF-$d_8$ (prepared from 1.0 equiv of oxazolinyoxirane **1** and 1.0 equiv of *s*-BuLi) was run at 203 K. At this higher concentration and temperature, the most striking difference concerned the $^{7}$Li NMR spectrum (Figure 8b) in which an enhancement of the resonance intensities of both two average broad peaks at $\delta$ 0.26 and 0.45 occurred, whereas the main peak at $\delta$ 0.77 broadened at both sides. The sample was then diluted with 0.8 mL of THF-$d_8$ in order to obtain a 0.08 M solution and run again at 203 K. Lower concentrations should lead, in principle, to slower interaggregate exchange as well as to break down higher aggregates into smaller ones. As is evident from Figure 8c, the corresponding $^{13}$C NMR spectrum now was apparently more simplified, in particular within the range of 30.0−32.0 ppm and around 70.0 ppm. Moreover, what was most notable is that, upon dilution of the solution, the broad signal related to the carbanionic carbon (C5) at $\delta$ 93.2 resolved into a very broad quartet of almost 1:1:1:1 intensity ($^{7}$Li $I$ 3/2) (Figure 8c). A careful examination of its shape suggested that two overlapping 1:1:1:1 quartets ($^{1}J_{13C\text{-}7Li} \approx 29.0$ Hz for both) may actually be involved instead; their poor resolution may probably be related to fast quadrupole-induced relaxation of the $^{7}$Li

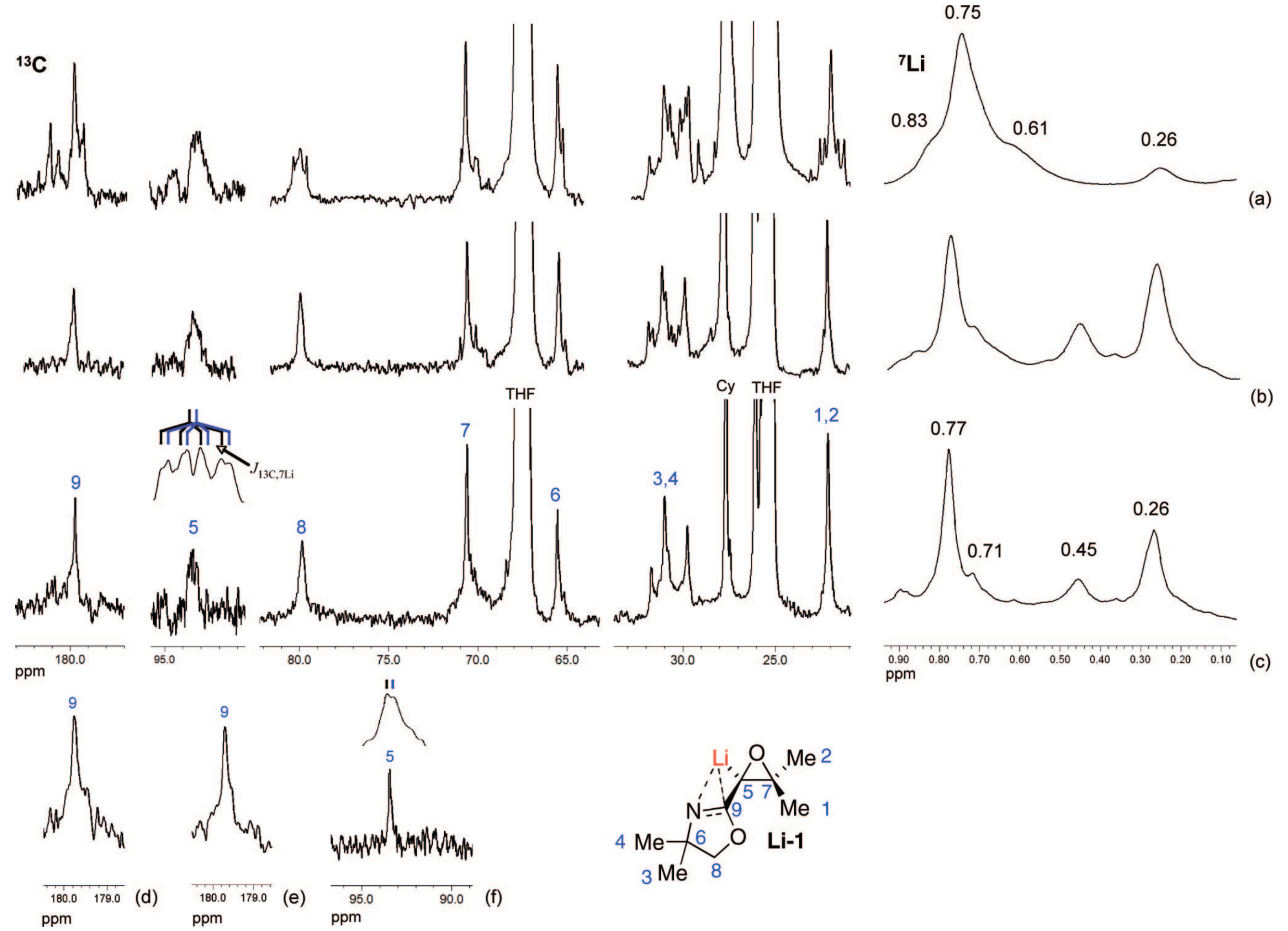

**FIGURE 8.** (a) $^{13}$C and $^{7}$Li NMR spectra of 0.6 M **Li-1** in THF-$d_8$ at 203 K. (b) $^{13}$C and $^{7}$Li NMR spectra of 0.3 M **Li-1** in THF-$d_8$ at 203 K. (c) $^{13}$C and $^{7}$Li NMR spectra of 0.08 M **Li-1** in THF-$d_8$ at 203 K. (d) The $^{13}$C NMR signal of the iminic carbon C9 of **Li-1** (0.08 M, THF-$d_8$, 203 K). (e) The $^{13}$C{$^{1}$H, $^{7}$Li} NMR signal of the iminic carbon C9 of **Li-1** (0.08 M, THF-$d_8$, 203 K). (f) The $^{13}$C{$^{1}$H, $^{7}$Li} NMR signal of the lithiated carbon C5 of **Li-1** (0.08 M, THF-$d_8$, 203 K). The insert in (f) is a Gaussian enhanced spectrum (LB = −1). All spectra were measured at natural abundance lithium and carbon.

nucleus.[30] To be sure that the fine structure exhibited by the peak at $\delta$ 93.2 under dilution conditions was due only to $^{13}$C,$^{7}$Li couplings, a triple-resonance experiment, $^{13}$C{$^{1}$H,$^{7}$Li}, was run on the same sample: the two overlapped broad quartets collapsed to give two overlapped broad singlets (Figure 8f). Interestingly, the $^{7}$Li decoupling also affected the line width of the iminic signal (C9): in fact, the line width at half-height changed from a value of $\Delta\upsilon_{1/2} = 68$ Hz to a value of $\Delta\upsilon_{1/2} = 37$ Hz before and after $^{7}$Li decoupling, respectively (Figures 8d,e). This fact is suggestive of a coupling occurring between the iminic carbon and $^{7}$Li as well, so supporting the hypothesis that an intra/intermolecular lithium $\pi$-coordination may be actually under way for the aggregates of **Li-1**. Indeed, in Stucky's view,[31] these organolithium $\pi$-complexes may be interpreted in terms of "multicenter covalent interactions between the unoccupied atomic orbitals of lithium and the appropriate occupied molecular orbitals of the hydrocarbon anion", even if ionic interactions are thought to dominate.[32] These results are suggestive of the possible coexistence of at least two type of aggregates each having a carbon directly coupled to only one lithium atom, such as it would occur either in a monomer intramolecularly $\eta^3$-coordinated ($\eta^3$-**M**) or in an oxazoline-bridged dimer (**D**) in which each lithium atom of a unit interacts with the $\pi$ iminic system of another unit (Scheme 4). It is worth noting that, after the sample was diluted from 0.3 to 0.08 M, in the $^{7}$Li NMR spectrum, peaks at $\delta$ 0.26, 0.45, 0.71 underwent a decrease in their resonance intensities with respect to the main one at $\delta$ 0.77, which was also simplified at the left side between 0.82 and 0.86 ppm (Figure 8c). These findings suggest that all of the species related to the above peaks should be "more aggregated" than that at $\delta$ 0.77, which was tentatively assigned to the $\eta^3$-monomer. Unfortunately, the strong overlapping occurring between peaks in both $^{13}$C and $^{7}$Li NMR spectra made a correlation between concentrations and integrals impractical. Now, the question is what about the nature of these several "more aggregated" species coexisting in equilibrium in solution with the monomer? In consideration of the fact that variable temperature studies suggested that intramolecular association may be probably playing an important role in dynamic equilibria under way and in order to justify the complexity of $^{7}$Li NMR spectra, we interpret the broad quartet (Figure 8b) related to a

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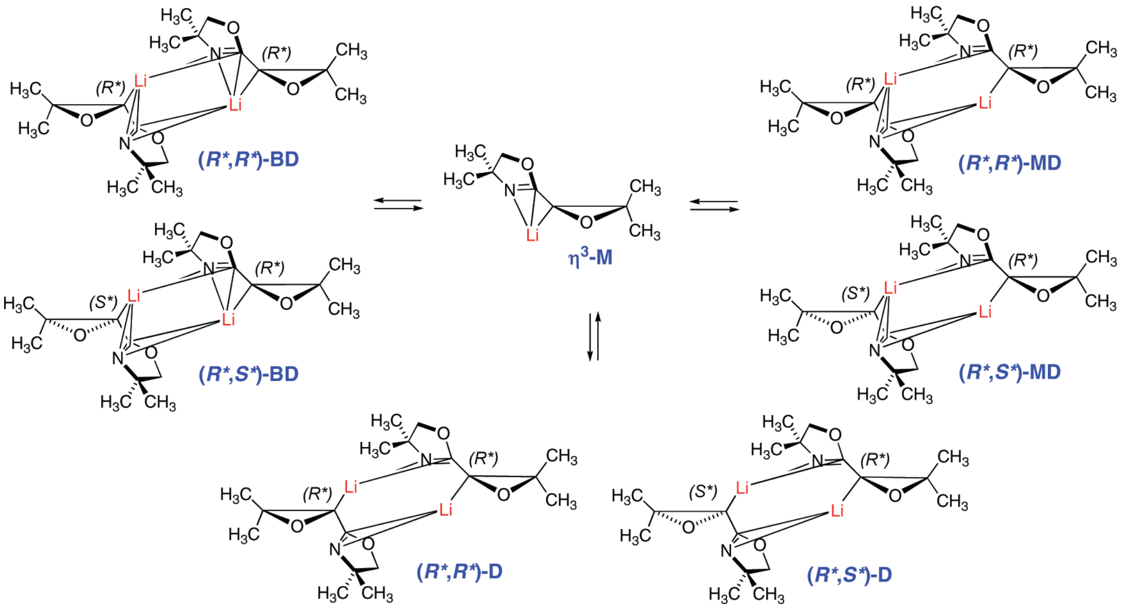
[30] (a) Fraenkel, G.; Subramanian, C.; Chow, A. *J. Am. Chem. Soc.* **1995**, *117*, 6300–6307. (b) Fraenkel, G.; Fraenkel, A. M.; Geckle, M. J.; Schloss, F. *J. Am. Chem. Soc.* **1979**, *101*, 4745–4747.

[31] Stucky, G. In *Polyamine-Chelated Alkali Metal Compounds*; Langer, A. W., Ed.; American Chemical Society: Washington, DC, 1974; Adv. Chem. Ser. No. 130, Chapter 3.

[32] Setzer, W.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353–451.

SCHEME 4



plausible oxazoline-bridged dimer as the average signal "representative" of a mixture of dimers, similar to **D**, but differently *intra*aggregated, each in a fast equilibrium with the monomeric species. One or both aza-allyl monomeric units may, indeed, benefit from an additional intramolecular $\eta^3$-coordination to give a mono- (**MD**, Scheme 4) or a bis-symmetrical (**BD**, Scheme 4) double-bridging arrangement with the two lithium atoms, respectively.[33] In addition, each of the above dimers may be present in solution as a mixture of homochiral or heterochiral diastereomers. Being $^7$Li nuclei homotopic in homochiral dimers ($R^*$,$R^*$)-**D** and ($R^*$,$R^*$)-**BD** but enantiotopic in heterochiral dimers ($R^*$,$S^*$)-**D** and ($R^*$,$S^*$)-**BD**, these aggregates should each exhibit a different $^7$Li signal. On the other hand, four distinct $^7$Li signals would be expected for the two homochiral and heterochiral dimers ($R^*$,$R^*$)-**MD** and ($R^*$,$S^*$)-**MD**, as each does have two diastereotopic $^7$Li nuclei. In principle, also considering the **$\eta^3$-M** monomer, up to nine signals may be observed in the corresponding $^7$Li NMR spectrum. Actually, the $^7$Li NMR spectrum of a 0.2 M sample of **Li-1** consists, at 160 K, of just nine peaks partially overlapped (Figure 7), even if the coexistence of other aggregates at this higher concentration cannot be completely discarded owing to the presence, in the $^{13}$C NMR spectrum, of minor species. In order to better investigate this aspect, we decided to check a sample of **Li-1** at a higher concentration than 0.3 M. Surprisingly, at a 0.6 M concentration, both $^7$Li and $^{13}$C NMR spectra of **Li-1** changed drastically (Figure 8a). In the $^7$Li NMR spectrum, the previous broad peaks at $\delta$ 0.26, 0.45, 0.71 (Figure 8b) did not increase their resonance intensity but instead, together with other smaller ones around 0.86−0.90 ppm, collapsed in favor of two broad shoulders at $\delta$ 0.61 and 0.83 on both side of the main broad peak, whose resonance appeared to be highfield shifted by 0.02 ppm ($\delta$ 0.75). In the $^{13}$C NMR spectrum, more complex patterns are discernible around the previous main average signals. In particular, at least four other peaks on both side of the average signal at $\delta$ 22.1 (C1,C2 resonances) together with a new carbanionic carbon, as a broad peak at $\delta$ 94.5, and other sets of iminic carbons more downfield shifted than 180 ppm could be detected. These results are suggestive of the possible formation of higher aggregated oligomers generated, most probably, at the expense of the aforementioned dimers, so supporting the hypothesis that intermolecular as well as intramolecular associations are the key aspects of the reactivity of **Li-1**. However, this new "picture" occurring at a higher concentration was not further investigated. Therefore, we conclude that the **Li-1** species may be present, at least in a range of concentration of 0.08−0.3 M, mainly as a **$\eta^3$-M** monomer in fast equilibrium, on the NMR time scale, with a complex mixture of variously *intra*aggregated diastereomeric oxazoline-bridged dimers (**D**, **MD** and **BD**) (Scheme 4). However, the higher the concentration is, the more competitive is the formation of higher aggregates.

Interestingly, a recent paper[34] claimed an inverse dependence of $^1J_{\mathrm{C,Li}}$ on the sum of the numbers of carbanion centers and coordinating electron-pair donating ligands, that is, a strong correlation between $^1J_{13\mathrm{C},7\mathrm{Li}}$ and the microsolvation of an organolithium compound. Having detected a similar value (ca. 29 Hz) for the $^1J_{13\mathrm{C},7\mathrm{Li}}$ coupling constant relative to the two type of aggregates mainly present at higher dilution (the $\eta^3$-monomer and the oxazoline-bridged dimer, each having a carbanionic carbon coupled to only one lithium), it is reasonable that the THF-microsolvation for both may be the same.

**Proposed Racemization Mechanism for Li-1.** On the basis of the above spectroscopic results, the configurational instability experimentally ascertained for oxiranyllithium **Li-1** may be tentatively interpreted as follows. At least in a range of concentration of 0.08−0.3 M, a multinuclear magnetic resonance investigation suggests that oxiranyllithium **Li-1** would mainly

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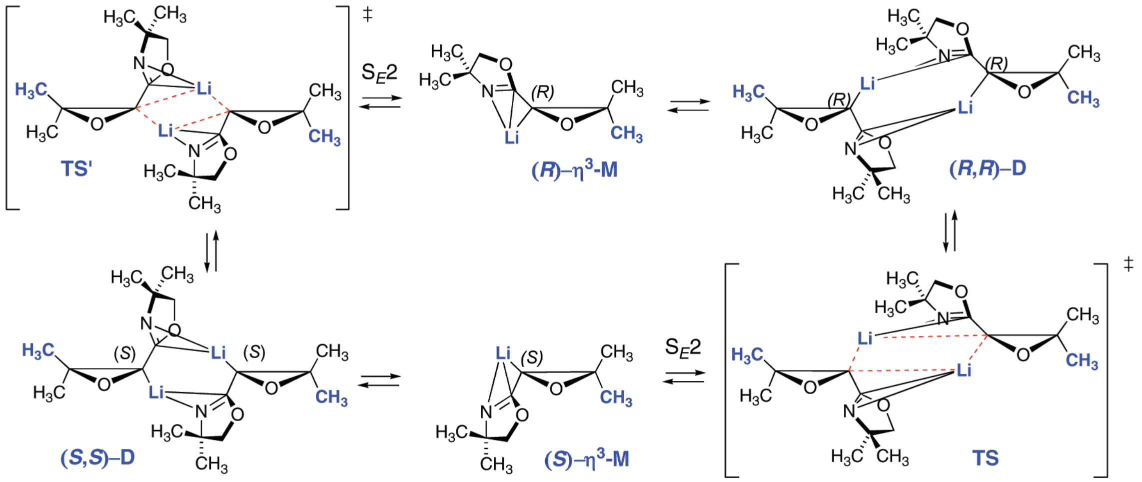
(33) For examples of other mono and double lithium($\eta^3$-aza-allyl)-type complexes, see: (a) Colgan, D.; Papasergio, R. I.; Raston, C. L.; White, A. H. *J. Chem. Soc., Chem. Commun.* **1984**, 1708–1710. (b) Hacker, R.; Schleyer, P. V. R.; Reber, G.; Müller, G.; Brandsma, L. *J. Organomet. Chem.* **1986**, *316*, C4–C8. The case of a dimer containing two diazallyl moieties, one of which acting as a double bridge of two lithiums, has been reported: (c) Eisen, M. S.; Kapon, M. *J. Chem. Soc., Dalton Trans.* **1994**, 3507–3510.

(34) According to an empirical expression proposed by the authors, the possibility of determining the unknown microsolvation number for the aggregation state of an organolithium compound from $^1J_{\mathrm{CLi}}$ requires knowledge not only of its aggregation state but also of a sensitivity factor related to the nature of the organolithium. However, for α-oxygen-substituted organolithium compounds, sensitivity factors have not been determined: Knorr, R.; Menke, T.; Ferchland, K.; Mehlstäuble, J.; Stephenson, D. S. *J. A. Chem. Soc.* **2008**, *130*, 14179–14188.

**SCHEME 5. Indirect Dynamic Interconversion between Two Lithiated $\eta^3$-Aza-allyl Enantiomeric Monomers**



exist in a THF solution as two $\eta^3$-aza-allyl enantiomeric monomers [(*R*)-$\boldsymbol{\eta}^3$**-M** and (*S*)-$\boldsymbol{\eta}^3$**-M**, Scheme 5] rapidly interconverting on the NMR time scale and each one in equilibrium with a complex mixture of diastereomeric oxazoline-bridged dimeric aggregates (**D**, **MD**, **BD**, Scheme 4). Their interconversion may be mediated by just one of the above detectable dimeric intermediates through a possible inversion transition state (**TS**) within which the two enantiomeric monomeric units would interchange their Li atoms in such a way that each lithium atom of a monomer would produce a $S_E2$-like rear-side attack on the carbanionic carbon atom of the other with the final result of an inversion of configuration (Scheme 5).[35] Among the various dimeric aggregates, one may speculate that a dimer such as **D** could be a good candidate in promoting the above racemization because, owing to its minor intramolecular association, a fewer number of bonds would need to be broken in the transition state on the way to inversion, so that, further to the $S_E2$ attack, an intermolecular $\pi$-deaggregation would be only followed by a new intramolecular $\eta^3$-coordination for each unit. Starting from a pure enantiomer, such as (*R*)-$\eta^3$**-M**, a homochiral dimer, such as (*R*,*R*)-**D**, would be most probably involved in the first equilibration to give, through the transition state **TS**, the enantiomer (*S*)-$\eta^3$**-M**. The latter would then equilibrate with the enantiomeric dimer (*S*,*S*)-**D**, which through the inversion transition state **TS′** would furnish again the enantiomer (*R*)-$\eta^3$**-M**.[36]

## Conclusions

In summary, α-lithiated oxazolinyloxirane **Li-1** was proved to be configurationally unstable in ethereal solvents on either the macroscopic or the microscopic time scale at −98 °C. Under the conditions of the Hoffmann test, which is based on kinetic resolution, **Li-1** underwent enantiomer equilibration at −98 °C with a rate comparable to that of its addition to *N*,*N*-dibenzylphenylalaninal. In addition, an optically pure sample of **1**, once deprotonated, racemized soon after its generation at −98 °C in THF and within 1 min at −130 °C in THF/Et$_2$O (3:2) ($t_{1/2} = 6.05$ s); the application of the Eyring equation suggested a barrier to inversion for **Li-1** of 8.8 kcal/mol at −130 °C. Notwithstanding its configurational instability, oxiranyllithium **Li-1** exhibited an unusual thermal stability; in fact, it underwent a successful deuterium incorporation (>98% D, 85% yield) even at 25 °C, the main side reaction being in THF a ring-opening reaction to give the keto-oxazoline **3**, in particular upon warming the reaction mixture to room temperature. Both in situ IR and NMR spectroscopy were employed to investigate the structure and dynamics of **Li-1** in solution. IR-spectroscopic studies showed that lithiation of **1** is complete at −98 °C within 1 min and is accompanied by a decrease of the C=N wavenumber by only 60 cm$^{-1}$, so supporting the idea that lithiated compound **Li-1** mainly exists in a THF solution and at low temperature (−98 °C) not as an azaenolate but as a true organolithium. The strong bias **Li-1** has to give rise to both intramolecular as well as intermolecular trihapto coordinations is the key point of its reactivity. A multinuclear magnetic resonance study suggested that several $\eta^3$-aza-allyl coordinated species might be most probably involved in dynamic equilibria in a THF solution at 170 K.[37] Dilution as well as variable-temperature studies also suggested that **Li-1** would be mainly present in a THF solution, at least in a range of concentration of 0.08−0.3 M, as a $\eta^3$-aza-allyl monomer in fast equilibrium, on the NMR time scale, with a complex mixture of diastereomeric oxazoline-bridged dimeric species variously *intra*aggregated. At higher concentration close to 0.6 M, **Li-1** may organize in higher oligomeric aggregates. An exchange mechanism, responsible for the fast racemization **Li-1** undergoes on the NMR time scale once generated, has been proposed. Powerful NMR techniques, such as the employment of diffusion-ordered NMR spectroscopy (DOSY), together with ab initio calculations and the use of labeled reagents, seem to be useful and complementary experimental approaches for a complete elucidation of the solution structure of **Li-1** at different levels of concentration; results will be reported in due course.

## Experimental Section

**General.** See Supporting Information.

**In Situ IR Spectroscopy.** In situ IR experiments were conducted with a ReactIR 4000 spectrometer equipped with K6 conduit and 5/8″ DiComp insertion probe (ASI Comp Technology, Mettler Toledo). The data points displayed per spectrum were collected with 45 scans every 30 s, resolution 8 cm$^{-1}$. The background spectrum was recorded in neat THF. The reaction was carried out

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[35] Schlosser, M. In *Organoalkali Chemistry, Organometallics in Synthesis A Manual*, 2nd ed.; Schlosser, M., Ed.; Wiley & Sons: New York 2004; p 32.

[36] It is worth noting that in the case of $^6$Li$^{13}$CH$_3$ and $^6$Li$^{13}$CCH$_2$SC$_6$H$_5$, an exchange mechanism by which monomers would interchange C and Li atoms via a nonobserved dimeric intermediate has been also proposed: Heinzer, J.; Oth, J. F. M.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1848–1862.

as follows: the flask, fitted with a magnetic stirring bar and under $N_2$ atmosphere, was charged with THF (4 mL), and oxazolinyloxirane **1** (169 mg, 1 mmol) was introduced after 11 acquisitions. TMEDA was added after the 20th acquisition (0.150 mL, 1 mmol, 1 equiv). After 24 acquisitions, the reaction mixture was cooled to −98 °C (liquid $N_2$/MeOH bath), and after the 43th (21 min elapsed) *s*-BuLi was added (0.77 mL, 1 mmol) at the same temperature. The mixture was finally quenched with excess MeOD after 84 acquisition (almost 80 min as the whole reaction time) and warmed to room temperature.

**NMR Spectroscopy: General Information.** NMR experiments were performed in Wilmad tubes (5 mm) fitted with a Wilmad/Omnifit Teflon valve assembly (OFV) and a Teflon/silicon septum. All NMR spectra were acquired using nonspinning 5 mm samples with deuterium field-frequency locking on a spectrometer equipped with a direct custom built 5 mm $^1H$, $^7Li-^{31}P$, $^{13}C$ triple-resonance probe-head including a *z*-gradient coil at the following frequencies: 599.944 MHz ($^1H$), 150.856 MHz ($^{13}C$), and 233.161 MHz ($^7Li$). $^{13}C$ NMR spectra were referenced internally to the C−O carbon of THF-$d_8$ ($\delta$ 67.45). Exponential multiplication (LB) of 2−6 Hz was applied to $^{13}C$ spectra. Quantitative $^{13}C$ NMR measurements were performed according to the inverse gated $^1H$-decoupling technique[38] with the composite pulse decoupling applied only during the short acquisition time and not during the delay (d1 = 10 s), which was at least 10 times the acquisition time. The typical pulse widths for 90° pulses ($\mu$s) and attenuation levels (dB, in brackets) were the following: $^{13}C$, 12.50 (3.50). $^7Li$ spectra were referenced externally to 0.3 M LiCl in MeOH-$d_4$ ($\delta = 0.0$). The typical pulse widths for 90° pulses ($\mu$s) and attenuation levels (dB, in brackets) were the following: $^7Li$, 15 (1.50); $^7Li$-dec, 100 (18). The probe temperature was calibrated using a methanol thermometer.

**NMR Spectroscopy: Representative Procedure for the Preparation of 0.2 M Sample of Oxiranyllithium Li-1 at −78 °C.** An appropriate amount of *s*-BuLi (77 $\mu$L, 0.1 mmol, 1.3 M in cyclohexane), first filtered over celite, was concentrated under reduced pressure in an NMR tube (assembled as described and previously evacuated and purged with argon) and the residual oil dissolved in THF-$d_8$ (0.3 mL) at −78 °C (acetone/dry ice bath). In a separate small flask, a weighed amount (17 mg, 0.1 mmol) of **1** was solubilized in THF-$d_8$ (0.2 mL), and the resulting solution was then slowly added by a gastight syringe to the solution of *s*-BuLi. The resulting reaction mixture was then shaken and immediately put in the NMR probe precooled to −78 °C.

**1-(4,4-Dimethyl-2-oxazolin-2-yl)-2-methyl-1,2-epoxypropane (1).** This compound was prepared according to the procedure previously described.[39] A chromatographic separation of the two enantiomers was set up on an analytical chiral stationary HPLC phase (Chiralpack IA, hexane/*i*-PrOH 90/10 v/v, flow rate 1.00 mL/min, detector UV at 220 nm, $k_1 = 0.46$ and $\alpha = 1.60$; see also Supporting Information) and then quantitatively carried out on the same preparative chiral stationary HPLC phase. First eluted enantiomer (+)-**1**: $[\alpha]^{20}_D = +7.5$ (*c* 1, $CHCl_3$), ee >99.9%. Second eluted enantiomer (−)-**1**: $[\alpha]^{20}_D = -7.5$ (*c* 1, $CHCl_3$), ee = 99.5%.

**1-Deuterio-1-(4,4-dimethyl-2-oxazolin-2-yl)-2-methyl-1,2-epoxypropane (1-D).** To a solution of **1** (169 mg, 1.0 mmol) in 5 mL of THF, precooled to −78 °C under $N_2$ and magnetic stirring, was slowly added *s*-BuLi (0.85 mL, 1.1 mmol, 1.3 M in cyclohexane). After stirring for 10 min at −78 °C, the reaction mixture was quenched with 0.2 mL of $CH_3OD$. The mixture was then allowed to room temperature, diluted first with 10 mL of $Et_2O$ and then with 10 mL of brine, and the two phases were separated. The aqueous phase was extracted with $Et_2O$ (3 × 10 mL), and the combined organic phases were dried with $Na_2SO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/$Et_2O$ 8/2) afforded deuterated oxirane **1-D** (160 mg, 94% yield, >95% D).

**1-(4,4-Dimethyl-2-oxazolin-2-yl)-2-methylpropan-1-one (3).** To a solution of **1** (84.5 mg, 0.5 mmol) in 3 mL of THF precooled to −78 °C, under $N_2$ and magnetic stirring, was slowly added *s*-BuLi (0.38 mL, 0.55 mmol, 1.3 M in cyclohexane). After stirring for 15 min at −78 °C, the reaction mixture was allowed to warm to room temperature and after 10 h was quenched with saturated aqueous $NH_4Cl$ and extracted with $Et_2O$ (3 × 10 mL); the combined organic phases were dried with $Na_2SO_4$ and concentrated under reduced pressure. Flash chromatography on silica gel (petroleum ether/$Et_2O$ 9/1) afforded keto-oxazoline **3** (65 mg, 77% yield) as a colorless oil. $^1H$ (600 MHz, $CDCl_3$): $\delta$ 1.28 (d, $J = 6.2$ Hz, 6 H), 1.43 (s, 6 H), 3.52 (eptet, $J = 6.2$ Hz, 1 H), 4.14 (s, 2 H). This compound could be also efficiently prepared in 80% yield by lithiation (*n*-BuLi/TMEDA, $Et_2O$, −100 °C)−rearrangement of oxazolinyloxirane **1**, as reported.[15]

**Reaction of Oxiranyllithium Li-1 with *N*,*N*-Dibenzylphenylalaninal 6.** To a precooled solution (−98 °C, liquid $N_2$/MeOH bath) of 169 mg (1.0 mmol) of oxazolinyloxirane **1** in 5.0 mL of THF was added 0.85 mL of *s*-BuLi (1.1 mmol, 1.3 M in cyclohexane) under $N_2$. After stirring for 5 min at −98 °C, a solution of 394 mg (1.2 mmol) of racemic 2-(*N*,*N*-dibenzylamino)-3-phenylpropanal **6** in 3.0 mL of THF was added dropwise. The reaction mixture was then stirred for additional 20 min at −98 °C and finally quenched with 20 mL of saturated aqueous $NH_4Cl$ solution. After warming to room temperature, the mixture was diluted with 10.0 mL of $Et_2O$, and the two phases were separated. The aqueous phase was extracted with $Et_2O$ (3 × 20 mL), and the combined organic phases were dried with $Na_2SO_4$ and concentrated under reduced pressure to give 548 mg of a slightly yellowish oil. $^1H$ NMR of the crude indicated the complete disappearance of the starting oxirane. $^{13}C$ NMR indicated the presence of four diastereomers (**7a**−**d**) in a ratio of 49:19:19:13. Flash chromatography (silica gel) over a 15-cm column ($\varphi$ 5 cm) with petroleum ether/AcOEt 85/15 as the eluant furnished first the most abundant isomer ($R_f$ 0.35), then the second less abundant isomer ($R_f$ 0.25), and finally a mixture of the two least abundant isomers ($R_f$ 0.19) which were further separated on the same column with petroleum ether/AcOEt 90/10 as the eluant ($R_f$ 0.15 and 0.11).

Major diastereomer, presumably, (*R**,*S**,*S**)-**7a**: white solid, mp 132−133 °C ($Et_2O$), 44% isolated yield, $R_f$ 0.35 (petroleum ether/AcOEt 8/2). $^1H$ NMR (400 MHz): $\delta$ 0.85 (s, 3 H), 1.17 (s, 3H), 1.39 (s, 3 H), 1.59 (s, 3 H), 2.94 (dd, $J = 14.3$, 4.6 Hz, 1 H), 3.06 (dd, $J = 14.3$, 7.9 Hz, 1 H), 3.37 (ddd, $J = 7.9$, 6.1, 4.6 Hz, 1 H), 3.65 (d, $J = 13.9$ Hz, 2 H), 3.70 and 3.81 (2 × d, AB system, $J = 8.2$ Hz, 2 H), 3.72 (d, $J = 13.9$ Hz, 2 H), 4.01 (m, 1 H), 4.67 (br s, exchanges with $D_2O$, 1 H), 7.13−7.26 (m, 15 H). $^{13}C$ NMR (100 MHz, DEPT): $\delta$ 20.2 (*$CH_3$*), 20.8 (*$CH_3$*), 27.6 (*$CH_3$*), 28.8 (*$CH_3$*), 32.9 (*$CH_2$*), 53.8 (2 × *$CH_2$*), 61.7 (*CH*), 63.1 (*$C_q$*), 63.2 (*$C_q$*), 67.7 (*$C_q$*), 71.0 (*CH*), 78.1 (*$CH_2$*), 125.4 (*CH*), 126.4 (2 × *CH*), 127.9 (6 × *CH*), 128.9 (4 × *CH*), 129.5 (2 × *CH*), 139.8 (2 × *$C_q$*), 141.5 (*$C_q$*), 163.0 (*$C_q$*). ESI-MS: 521 [$M^+$ + 23 (Na)]. FT-IR (KBr, $cm^{-1}$) 3210, 3018, 2959, 1653 (C═N), 1601, 1493, 1363, 1294, 1070, 740, 698. Anal. Calcd for $C_{32}H_{38}N_2O_3$: C, 77.08; H, 7.68; N, 5.62. Found: C, 76.73; H, 7.77; N, 5.36.

First minor diastereomer, presumably, (*R**,*R**,*S**)-**7b**: white solid, mp 124−126 °C ($Et_2O$), 8%, $R_f$ 0.11 (EP/AcOEt 9/1). $^1H$ NMR (400 MHz): $\delta$ 1.03 (s, 3 H), 1.18 (s, 3 H), 1.32 (s, 3 H), 1.43 (s, 3 H), 2.86 (dd, $J = 13.1$, 1.9 Hz, 1 H), 3.14 (dd, $J = 13.1$, 3.8 Hz, 1 H), 3.40 (m, 1 H), 3.66 (d, $J = 15.7$, 2 H), 3.68 and 3.80 (2 × d, AB system, $J = 8.0$ Hz, 2 H), 3.76 (d, $J = 7.5$, 1 H), 4.10 (d, $J = 15.7$, 2 H), 4.77 (br s, exchanges with $D_2O$, 1 H), 7.00−7.05 (m, 4 H), 7.10−7.16 (m, 5 H), 7.27−7.33 (m, 6 H). $^{13}C$ NMR (100

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[37] One of the first $^{13}C$ NMR studies of chiral α-lithiated-2-alkyloxazolines was performed by Meyers et al., who demonstrated that in a THF solution, at low temperature, the above metalated intermediates do exist as nonequilibrating diastereomeric mixtures of azaenolates; see: Meyers, A. I.; Snyder, E. S.; Ackerman, J. J. H. *J. Am. Chem. Soc.* **1978**, *100*, 8186–8189. It is also interesting to note that for one of the above azaenolates, the $^{13}C$ NMR chemical shift reported for the C-2 oxazoline carbon was 168.5 ppm.

[38] Freeman, R.; Hill, H. D. W.; Kaptein, R. *J. Magn. Reson.* **1972**, *7*, 327–329.

[39] Perna, F. M.; Capriati, V.; Florio, S.; Luisi, R. *J. Org. Chem.* **2002**, *67*, 8351–8359.

MHz, DEPT): $\delta$ 20.9 ($CH_3$), 22.2 ($CH_3$), 28.1 ($CH_3$), 28.3 ($CH_3$), 33.5 ($CH_2$), 53.7 (2 × $CH_2$), 60.9 ($CH$), 63.5 ($C_q$), 64.6 ($C_q$), 67.6 ($C_q$), 71.8 ($CH$), 78.4 ($CH_2$), 125.9 ($CH$), 127.1 (2 × $CH$), 128.3 (4 × $CH$), 128.4 (2 × $CH$), 129.1 (4 × $CH$), 129.8 (2 × $CH$), 138.9 (2 × $C_q$), 140.3 ($C_q$), 160.6 ($C_q$). ESI-MS: 521 [$M^+ + 23$ (Na)]. FT-IR (KBr, $cm^{-1}$) 3271, 3027, 2964, 2925, 1666 (C=N), 1495, 1454, 1365, 1122, 1028, 744, 698. Anal. Calcd for $C_{32}H_{38}N_2O_3$: C, 77.08; H, 7.68; N, 5.62. Found: C, 76.91; H, 8.04; N, 5.33.

Second minor diastereomer, presumably, ($S^*$,$S^*$,$S^*$)-**7c**: white solid, mp 113−115 °C ($Et_2O$), 17% isolated yield, $R_f$ 0.25 (petroleum ether/AcOEt 8/2). $^1$H NMR (400 MHz): $\delta$ 1.09 (s, 3 H), 1.14 (s, 3 H), 1.33 (s, 3 H), 1.56 (s, 3 H), 2.91 (dd, $J$ = 14.2, 10.9 Hz, 1 H), 3.07−3.15 (m, 6 H), 3.48 (d, $J$ = 10.1, 1 H), 3.73 (d, $J$ = 8.2, 1 H), 3.78 (d, $J$ = 8.0, 1 H), 4.70 (br s, exchanges with $D_2O$, 1 H), 7.18−7.41 (m, 15 H). $^{13}$C NMR (100 MHz, DEPT): $\delta$ 19.6 ($CH_3$), 21.2 ($CH_3$), 27.8 ($CH_3$), 28.4 ($CH_3$), 33.7 ($CH_2$), 53.4 (2 × $CH_2$), 61.6 ($CH$), 62.6 ($C_q$), 63.2 ($C_q$), 67.0 ($C_q$), 71.4 ($CH$), 79.1 ($CH_2$), 126.3 ($CH$), 127.1 (2 × $CH$), 128.3 (4 × $CH$), 128.4 (4 × $CH$), 129.1 (2 × $CH$), 130.0 (2 × $CH$), 138.5 (2 × $C_q$), 140.3 ($C_q$), 162.0 ($C_q$). ESI-MS: 521 [$M^+ + 23$ (Na)]; FT-IR (KBr, $cm^{-1}$) 3352, 3027, 2966, 2927, 1663 (C=N), 1603, 1454, 1377, 1120, 1029, 750, 700. Anal. Calcd for $C_{32}H_{38}N_2O_3$: C, 77.08; H, 7.68; N, 5.62. Found: C, 76.83; H, 8.01; N, 5.45.

Third minor diastereomer, presumably, ($S^*$,$R^*$,$S^*$)-**7d**: white solid, mp 121−122 °C ($Et_2O$), 14%, $R_f$ 0.15 (petroleum ether/AcOEt 9/1). $^1$H NMR (400 MHz): $\delta$ 0.98 (s, 3 H), 1.11 (s, 3 H), 1.37 (s, 3 H), 1.66 (s, 3 H), 2.38−2.44 (m, 1 H), 2.86 (dd, $J$ = 13.5, 1.9 Hz, 1 H), 3.01 (d, $J$ = 8.2 Hz, 1 H), 3.03−3.12 (m, 2 H), 3.64 (d, $J$ = 15.1 Hz, 2 H), 3.71 (d, $J$ = 8.2 Hz, 1 H), 4.11 (d, $J$ = 15.1, 2 H), 4.73 (br s, exchanges with $D_2O$, 1 H), 7.00−7.05 (m, 4 H), 7.10−7.16 (m, 5 H), 7.27−7.33 (m, 6 H). $^{13}$C NMR (100 MHz, DEPT): $\delta$ 19.1 ($CH_3$), 22.3 ($CH_3$), 27.5 ($CH_3$), 28.3 ($CH_3$), 31.8 ($CH_2$), 53.7 (2 × $CH_2$), 61.6 ($CH$), 62.9 ($C_q$), 64.5 ($C_q$), 67.2 ($C_q$), 71.9 ($CH$), 78.9 ($CH_2$), 125.9 ($CH$), 126.3 (2 × $CH$), 127.6 (2 × $CH$), 128.0 (4 × $CH$), 128.1 (4 × $CH$), 130.4 (2 × $CH$), 140.0 (2 × $C_q$), 140.1 ($C_q$), 161.5 ($C_q$). ESI-MS: 521 [$M^+ + 23$ (Na)]; FT-IR (KBr, $cm^{-1}$) 3272, 3062, 3028, 2966, 2926, 1668 (C=N), 1603, 1454, 1379, 1122, 1041, 744, 703. Anal. Calcd for $C_{32}H_{38}N_2O_3$: C, 77.08; H, 7.68; N, 5.62. Found: C, 76.71; H, 7.99; N, 5.45.

Using optically active ($S$)-2-($N$,$N$-dibenzylamino)-3-phenylpropanal **6**, the four adducts **7a**−**d** were obtained in almost the same diastereomeric ratio (50:20:19:11 by $^{13}$C NMR) and, after isolation, presented the following optical rotations: **7a** $[\alpha]^{20}_D = -49$ ($c$ 1, $CHCl_3$); **7b** $[\alpha]^{20}_D = -25$ ($c$ 1, $CHCl_3$); **7c**: $[\alpha]^{20}_D = -82$ ($c$ 1, $CHCl_3$); **7d** $[\alpha]^{20}_D = +16$ ($c$ 1, $CHCl_3$).

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**Supporting Information Available:** General (S2); copies of $^1$H and $^{13}$C NMR spectra for compounds **1-D** (S3), ($R^*$,$S^*$,$S^*$)-**7a** (S4), ($R^*$,$R^*$,$S^*$)-**7b** (S5), ($S^*$,$S^*$,$S^*$)-**7c** (S6), ($S^*$,$R^*$,$S^*$)-**7d** (S7); copy of $^1$H NMR spectrum of oxiranyllithium **Li-1** (S8); copy of phase-sensitive gHSQC-DEPT spectrum of oxiranyllithium **Li-1** (Figure S1, S9); copy of the HPLC chromatogram relative to the analytical separation of the two enantiomers (+)-**1** and (−)-**1** (Figure S2, S10); *xyz* coordinates (B3LYP/6-31+G*) relative to the two equilibrium geometries found for oxazolinyloxirane **1** (S11). This material is available free of charge via the Internet at http://pubs.acs.org.

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