

On the Dichotomic Reactivity of Lithiated Styrene Oxide: A Computational and Multinuclear Magnetic Resonance Investigation

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Abstract: A multinuclear magnetic resonance investigation, supported by density functional theory calculations, has been synergically used to investigate the configurational stability, reactivity and aggregation states of α -lithiated styrene oxide in THF at 173 K. NMR studies on α -lithiated [α,β - $^{13}\text{C}_2$]styrene oxide (also in an enantiomerically enriched form) proved that in THF this oxiranyllithium is mainly present as a solvated monomeric species in equilibrium with a complex mixture of stereoisomeric dimeric aggregates, as well as with bridged and tetrameric aggregates. The fact that some $\text{C}_\alpha\text{--Li}$ bonds are partial-

ly broken in some stereoisomers reduces their symmetry and complicates the NMR spectra: two diastereoisomers each having a pair of diastereotopic carbon atoms slowly inverting at the lithium atom in absence of tetramethylethylenediamine (TMEDA) have been detected. A ($^{13}\text{C}, ^7\text{Li}$)-HMQC experiment to correlate ^7Li and ^{13}C resonances of the various aggregates has been performed for the first time.


Keywords: carbenoids • density functional calculations • lithiation • NMR spectroscopy • oxygen heterocycles

From natural bond analysis, the monomeric aggregate was proven to have a lower carbenoid character with respect to bridged O-coordinated dimeric aggregates. The employment of suitable experimental conditions in terms of concentration, temperature and the presence or not of TMEDA are crucial to mitigate at the best the “carbene-like” reactivity of lithiated styrene oxide toward intermolecular C–Li insertions, eliminative dimerisation reactions and ring-opening reactions. A two-step mechanism for the deprotonation of styrene oxide by $s\text{BuLi}$ in THF has been proposed and discussed as well as competitive side reactions.

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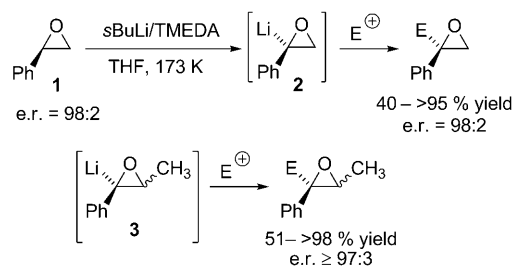
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 Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200900834>. It contains total energies (atomic units) (B3LYP/6-31+G(d) and B3LYP/6-311+G(d,p)) and Cartesian coordinates (B3LYP/6-31+G(d)) of neutral and lithiated styrene oxide (S3–S15); natural charge distribution analysis in neutral styrene oxide (S16); natural charge distribution analysis in free (**2a**) and solvated lithium styrene oxide (S17); comparison of selected geometrical parameters in free (**2a**, **4a** and **4c**) and solvated lithium salt (S18); natural charge distribution analysis in free and solvated dimer (**4c**) of lithium styrene oxide (S19); comparison of the theoretical and experimental ^{13}C NMR shieldings for neutral styrene oxide **1** (S20); theoretical ^{13}C NMR shieldings in free dimers (**4**) and solvated lithium salt (S20); natural bond orbital energies of $\sigma_{\text{O--Ca}}$ and $\sigma^*_{\text{O--Ca}}$ orbitals in neutral and lithiated styrene oxide in different aggregates and solvated forms (S20); optimised structures for neutral **1** and side views of **4a–4d** (S21–S23); 1D and 2D NMR spectra (S23–S27); schematic drawings of additional aggregates (S27).

Introduction

Oxiranyllithium species are an amazing class of reactive intermediates, which today have been playing more and more a leading role in stereoselective organic synthesis.^[1] Since a direct lithiation of terminal epoxides can be successfully performed in absence of electron-withdrawing groups,^[2] this suggests that this kind of α -oxygen-substituted organolithium species have an “intrinsic stability”, presumably due either to the fact that oxygen substitution increases thermodynamic carbanion stability^[3] or that their β -eliminative decomposition (being the reverse of a 3-*endo*-trig cyclisation) may be disallowed according to the Baldwin’s rules.^[4] Their ring-opening reactions are, indeed, mainly dominated by alkylative deoxygenations (especially when organolithium species are used as lithiating agents),^[1a,c,f,g,j,5a-c] “homocoupling” reactions,^[1g,5d] selective isomerisations (e.g., with medium-sized cycloalkene oxides),^[1a,c,f,j,6] 1,2-H (alkyl, aryl) shifts,^[1a,c,f,j] all referable to the well-known carbenoid nature^[1f,7] of these reactive intermediates. However, despite the growingly application in stereoselective synthesis of oxiranyllithium species,^[1d,h-j,8] their structural features remain a matter of interpretation. Many questions are still unanswered, such as the role played by the so-called “stabilizing” substituents: do they simply enhance the acidity of the adjacent C–H epoxide bond or are they really able to delocalise the incipient negative charge formed upon deprotonation?^[9] And, if this is the case, how could configurational stability sometimes be observed? Since the factors affecting their reactivity and related mechanisms are not well understood, it is of crucial importance to study their solution structure for the optimisation of their coupling reactions with electrophiles. So far, only a few detailed rate studies of LiTMP- and LDA-mediated (LiTMP = lithium tetramethylpiperide; LDA = lithium diisopropylamide) lithiation of epoxides have been reported by Collum’s group.^[10] The structure, configurational stability and stereodynamics in solution of α -lithiated 3,3-dimethyl-2-oxazolinylloxirane have recently been investigated by our group by means of in situ IR and NMR spectroscopy.^[11] Interestingly, oxiranyl anion methodology has also recently been applied to preparative scale synthesis of substituted epoxides by taking advantage of microflow systems, which also served as a powerful tool for mechanistic studies.^[12] Our concerns in the oxiranyllithium field, aimed at making more functionalised epoxides,^[1d,g,j,13] led us to the observation that lithiated styrene oxide^[14] **2**, among other oxiranyllithium species, could be generated by treating its precursor **1** with *s*BuLi/tetramethylethylenediamine (TMEDA) in THF and successfully and stereospecifically trapped with electrophiles to give more substituted styrene oxides with retention of configuration at the benzylic carbon atom (Scheme 1). Likewise, highly stereospecific were the coupling reactions with electrophiles of lithiated *trans*- and *cis*-3-methyl-2-phenyloxiranes^[15] **3**, which also exhibited a higher thermal stability (Scheme 1).^[16] This is an indication of a *carbanionic* behaviour exhibited by such reactive intermediates at low temperature in THF. In contrast,



Scheme 1. Deprotonation of styrene oxide **1** and quenching of anions **2** and **3** with electrophiles.

if a longer reaction time (particularly in the case of lithiated styrene oxide), a higher temperature or a nondonor solvent are employed, their *carbenoid* character^[17] comes into play.

Now, the questions are: how strong is this carbenoid character in ethereal solvents? What are the factors responsible for such a “carbene-like” reactivity? Is the “same species” able to exhibit an ambiphilic behaviour according to the employed experimental conditions or could “different species” be involved instead? In this paper, we will deal with the solution structure and the nature of lithiated styrene oxide **2** as well as the role played by the phenyl group, the base, the solvent, the temperature and the ligand (TMEDA) on its formation and “stabilisation”. Computational studies supporting multinuclear magnetic resonance investigations have been carried out with the aim of furnishing a plausible explanation about the “factors” responsible for the two facets of the reactivity of this lithiated species: the carbanionic or the carbenoid character.

Results and Discussion

Computational studies: First of all, to gain further insights about the nature and the reactivity of this lithiated system, a computational investigation at the B3LYP/6-31+G(d) level of theory on neutral **1** and lithiated styrene oxide **2** was undertaken.^[18,19] The natural charge analysis^[20] on the neutral styrene oxide **1** shows that charges on phenyl and oxirane ring are almost neutral (see Figure S1 and Table S1 in the Supporting Information).

Free lithium salt: In the free lithium salt (Figure 1), the lithium ion has a +0.91 positive charge, counterbalanced by a –0.91 negative charge on the organic anionic system. However, the negative charge is slightly delocalised onto the phenyl ring, being mostly resident on the oxirane ring (–0.77; Table S2 in the Supporting Information). This is likely the consequence of the sp^3 -like nature of the deprotonated carbon atom, with low overlap with the phenyl π system. Computed bond-lengths and π charges support this conclusion (Table S3 in the Supporting Information). The total phenyl π charge is increased by only 55 me upon deprotonation. It should be noted that, in line with the litera-

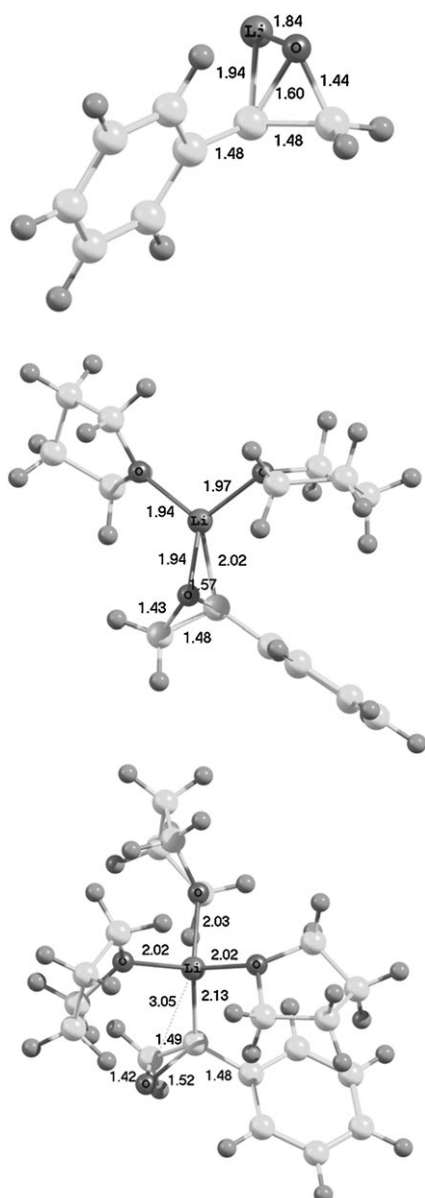


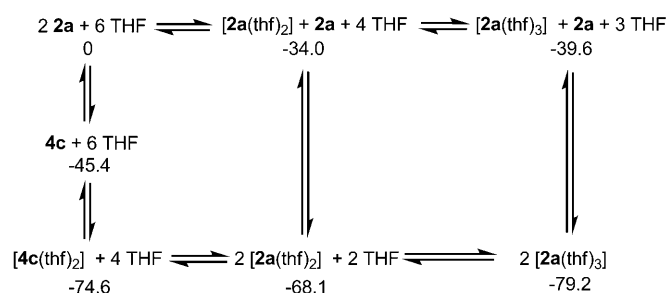
Figure 1. B3LYP/6-31+G(d) optimised structures of free (**2a**; top), di- (**[2a(thf)₂]**; middle) and tri-solvated (**[2a(thf)₃]**; bottom) lithiated styrene oxide **2**.

ture, the π charge on the *ipso*-carbon atom, directly linked to the carbanionic site, is positive.^[21]

Solvated lithium salt: Lithium coordination by two or three molecules of THF increases the negative charge delocalised onto the phenyl ring from 16 % (free species) to 25 % in the tri-solvated system.^[22] Accordingly, the π charge increases to -0.10 in the tri-solvated species from -0.05 in unsolvated **2a**. It is important to note that the increase of negative charge in the phenyl ring upon solvation is not simply due to the electron-donor properties of the solvent molecules, since the global negative charge increase of the lithium salt is smaller than that of the phenyl portion (Table S2 in the

Supporting Information). A total rearrangement of the electron structure takes place upon solvation that matches the geometric structural rearrangement (*vide infra*). Depending on the computed species, coordination between lithium and the oxirane oxygen may be either present or absent. As derived from bond lengths (Figure 1 and Table S3 in the Supporting Information), this interaction is present in the free and di-solvated species, but is no longer maintained when a third molecule of solvent is introduced. It should be noted that, either by coordination with oxirane oxygen or solvent molecules, the lithium ion reaches the tetracoordination both in the di- and tri-solvated salt. Similar behaviour was shown for the coordination of lithium enolates by ethereal solvents.^[23] Bond lengths for solvated compounds compare well those previously found for lithium enolates as well.^[23,24]

Solvation energies: As expected, the solvation energy strongly decreases from the first two solvations to the third one (Scheme 2). Whereas in the first two steps the average



Scheme 2. Dimerisation and solvation energies (in kcal mol⁻¹) calculated using B3LYP/6-311+G(d,p). Numbers refer to relative energy values with respect to the reference chemical species **2a**+6 THF. **4c** indicates the most stable dimeric aggregate (Figure 3).

energy per solvation is -17.0 kcal mol⁻¹, in the last step the energy is as little as -5.6 kcal mol⁻¹. This behaviour is the consequence of the saturation of the binding energies as the number of solvent molecules increases and is consistent with data reported in the literature for the solvation of the lithium cation,^[25] methyllithium,^[26] lithium amides,^[27] and lithium enolates.^[23,24] The binding energy of the third molecule of solvent is small but still important, considering the simultaneous loss of the interaction between the counterion and the oxirane oxygen. Therefore, the coordination with a third molecule of THF provides the system with a greater stability than that originating from the interaction with the oxirane ring. However, it should be considered that the solvation process is entropically unfavoured, since it reduces the freedom of motion. From literature data based on ¹³C and ⁷Li NMR studies on THF-solvated alkyllithium species,^[28] a contribution of about 5–10 eu per molecule of solvent can be extrapolated. At 173 K the entropic contribution of the third solvation step would at the most be approximately 2 kcal mol⁻¹, which is smaller than the energy gain, leading to a still negative ΔG value.

We can, therefore, conclude that the tri-solvated species, with no coordination between Li and the oxirane ring oxygen and with an almost tetrahedral arrangement around the carbanionic carbon, is the most stable species both on the basis of energy (ΔE) and Gibbs' energy (ΔG) data.

Free lithium dimer: Because of the high ionic character^[29] of the Li–C bond in lithiated styrene oxide, dipole–dipole attraction results in the formation of supermolecular aggregates.^[24] The balance between enthalpy gain in the formation of new bonds and entropy loss discriminates between solvation and aggregation. Four different bridged dimers (**4a–4d**) of lithiated styrene oxide were investigated (Figure 2).

The energy difference among all four isomers is about 1 kcal mol^{−1}, which indicates a possible equilibrating multitude of species simultaneously present. In the most stable isomer (**4a**), the lithium ion coordinates the oxirane oxygen and to two C_α atoms, one in each monomeric unit (Figure 2). This means that each C_α-carbon coordinates two lithium ions. The lithium atoms, oxirane oxygen atoms, and the C_α atoms form a nearly planar six-membered ring with the C_β atoms positioned on each side of this plane (see Supporting Information for side views, Figures S2–S5). The dimerisation does not affect the total delocalisation of negative charge into the phenyl ring of **4a**, which remains at 15%.^[30] This contrasts the observation of the role of solvation, in which an enhanced delocalisation into the phenyl ring resulted. The reaction energy for the formation of dimer **4a** from two monomers of **2a** is −45.4 kcal mol^{−1} at the B3LYP/6-311+G(d,p)^[31] level of theory. Thus, in a non-coordinating solvent as toluene, lithiated styrene oxide would appear as a dimer (or possibly a larger aggregate). However, accounting for the solvation energy from six THF molecules on two molecules of **2a** (in total −79.2 kcal mol^{−1}), indicates that the solvation will break the aggregate of lithiated styrene oxide into solvated monomers (Scheme 2). Can solvation of the dimer make a shift in this equilibrium?

Solvated lithium dimer: Upon solvation of the different dimeric isomers, it is found that di-solvated [**4c**(thf)₂] is the most stable (Figure 3). The energy difference between the different isomers is now increased to up to 3 kcal mol^{−1}. In a fully equilibrated solution of lithiated styrene oxide in THF at low temperature, this isomer of the dimer will be mainly observed. At elevated temperatures, it is more likely that a multitude of isomers are present. The solvation energy for solvation of isomer **4c** with two molecules of THF is found to be −29.2 kcal mol^{−1}. This solvation energy is somewhat smaller than that observed for the monomer, but it clearly compensates for the loss of translational entropy from the two solvent molecules. From these results, we can conclude that isomer **4c** will be explicitly solvated. When comparing the energies for [**4c**(thf)₂] and [**2a**(thf)₃], we find that the tri-solvated monomer is 4.6 kcal mol^{−1} more stable than the di-solvated dimer (Scheme 2). Taking into the account the

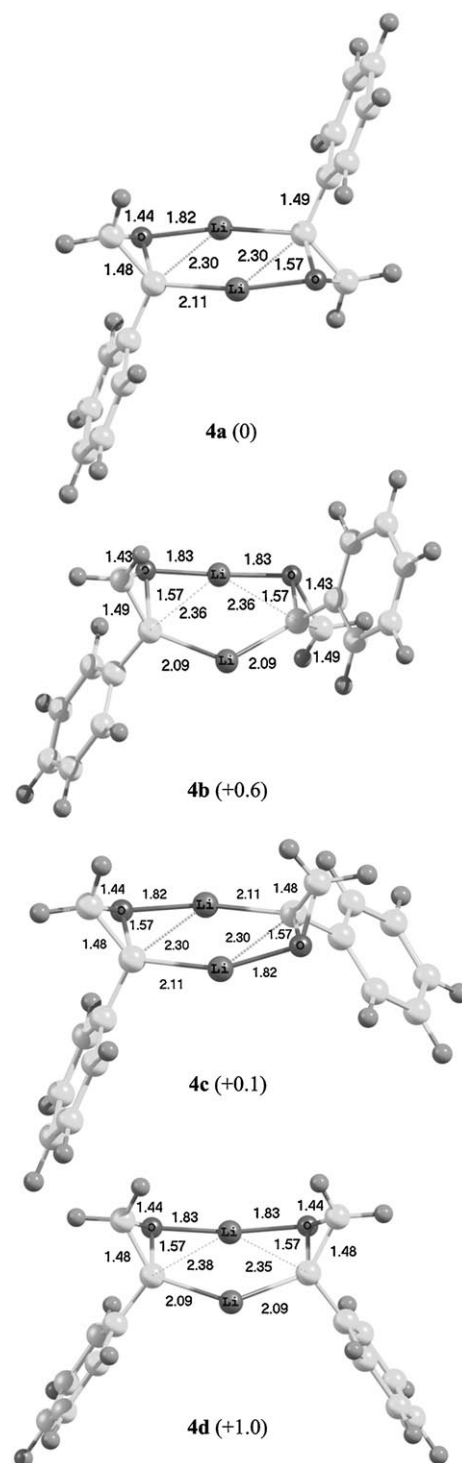


Figure 2. Optimised structures of the free lithiated dimers **4a–4d** of styrene oxide and relative energies (kcal mol^{−1}).

loss of entropy, in this comparison for three molecules at 173 K, it is most probable that the state including the dimer is the most preferred. The small energy difference and the accuracy of the method does not allow us to clearly distinguish which one of the two states that will be most populated. The main structural features of isomer [**4c**(thf)₂] are

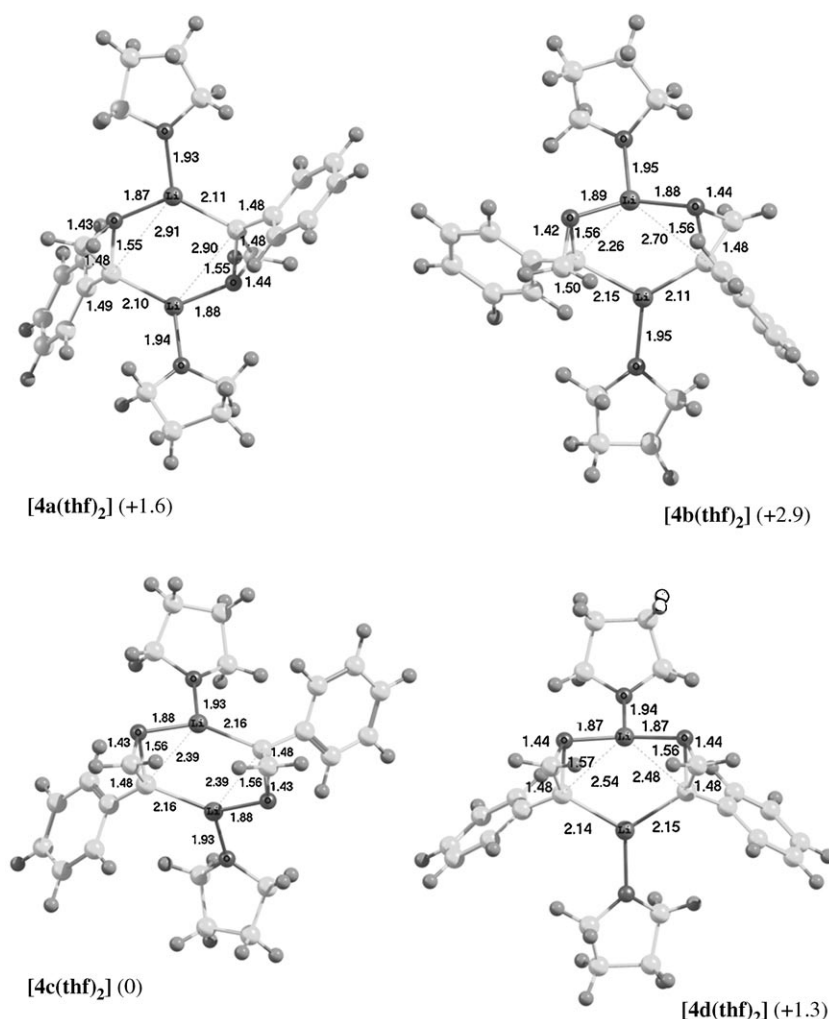


Figure 3. Optimised structures of the di-solvated lithiated dimers ([4a(thf)₂]-[4d(thf)₂]) of styrene oxide and relative energies (kcal mol⁻¹).

intact when THF is coordinated, although a minor elongation of the Li-O and Li-C_α bonds are observed (Figure 3 and Tables S3 and S4 in the Supporting Information). It is interesting to observe the structural features of some other isomers studied ([4a(thf)₂], [4b(thf)₂] and [4d(thf)₂], Figure 3). For example, one of the C_α-Li bonds in the isomer [4b(thf)₂] is partially broken; in fact, a C_α-Li distance of 2.70 Å can be viewed as only a partial interaction. As a fourth example, [4d(thf)₂] has two partially broken bonds with distances of about 2.5 Å.^[32]

The analysis of the solvated dimers **4** indicates that solvation increases the delocalisation of negative charge. In isomer [4c(thf)₂] about 20 % of negative charge is located in the phenyl rings (Table S4 in the Supporting Information), similarly as that observed for the solvated monomer **2a**. What contrasts the delocalisation in the solvated monomer and the solvated dimer is that, for the monomer, negative charge is taken about equally from the oxirane oxygen and the C_α carbon atoms, while in the dimer most of the negative charge is taken from the C_α carbon atom.

In conclusion, the structure and energy analysis indicate that in THF, lithiated styrene oxide may be present as a di-solvated dimer or as a tri-solvated monomer. In light of the small energy difference between the two most stable states, could we provide some more information to put into the two different scales of the balance and be able to decide on the *nature* and *aggregation state* of lithiated styrene oxide? To this end, we found it instructive to perform an NMR study.

¹³C, ¹H, ⁷Li and ⁶Li NMR spectroscopic studies—deprotonation of styrene oxide in the presence of TMEDA

¹H, ¹³C and ⁷Li NMR investigation in [D₈]THF at 173 K: NMR has proven to be powerful for studying the structure, bonding and dynamics of organolithium compounds in solution.^[33] Lithiated styrene oxide is a very reactive intermediate and NMR experiments have shown that it is kinetically stable in [D₈]THF in the presence or absence of TMEDA over a period of a few hours only if the temperature is rigorously kept at a value not higher

than 175 K. Lithiation of styrene oxide was performed with *s*BuLi.

This organolithium was found by Fraenkel to be a mixture of diastereomeric dimers, tetramers and hexamers that invert slowly at the lithiated carbon in cyclopentane (2M, 232 K),^[34] whereas in THF (1.2M, 177 K) Bauer detected two sets of signals consistent with a monomer-dimer equilibrium.^[35] A 0.2M solution of *s*BuLi in [D₈]THF at 173 K showed only one set of ¹³C NMR signals for the anionic species, the chemical shifts of which (δ = 39.7, 28.8, 19.4 ppm for the C-3, C-1 and C-4 carbon atoms, respectively) resulted to be very close to those reported by Bauer for the monomeric aggregate (Figure 4a).^[35] The anionic carbon (C-2) was hidden under [D₇]THF at δ = 25.7 ppm, as observed from a 2D ¹H,¹³C-HSQC-DEPT experiment (Figure S8 in the Supporting Information).

By adding a preformed mixture of styrene oxide (1 equiv) and TMEDA (1 equiv) in [D₈]THF to a precooled solution (173 K) of *s*BuLi (1.2 equiv) in [D₈]THF (0.2M, see Experimental Section), a new set of signals slowly emerged in both

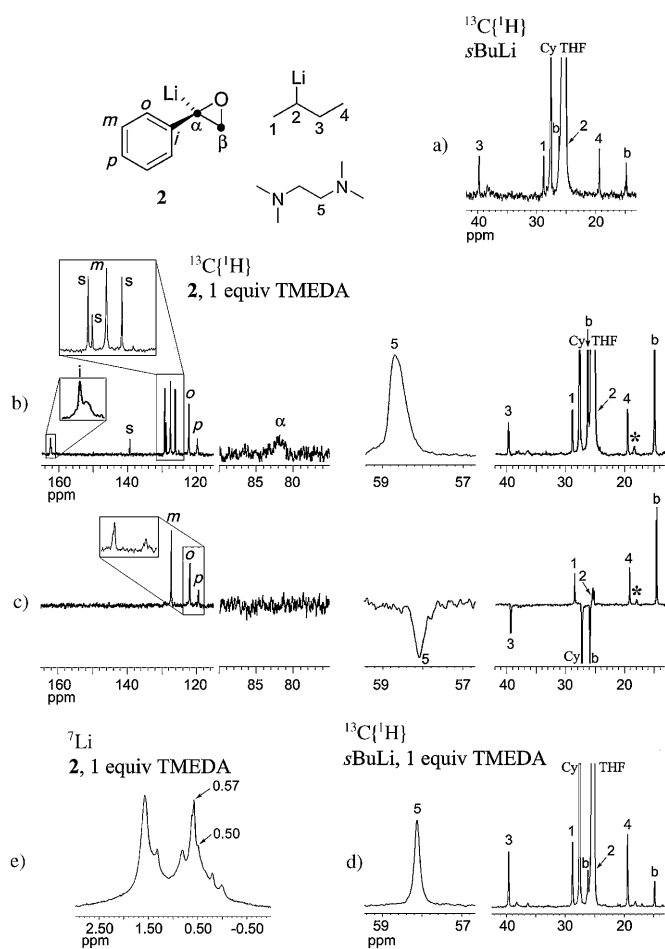


Figure 4. a) ^{13}C NMR spectrum of 0.2 M $s\text{BuLi}$ in $[\text{D}_8]\text{THF}$ at 173 K. b) ^{13}C NMR spectrum of 0.2 M **2** in $[\text{D}_8]\text{THF}$ at 173 K with one equivalent of TMEDA at the beginning of lithiation. c) DEPT-135 NMR spectrum of 0.2 M **2** in $[\text{D}_8]\text{THF}$ at 173 K with one equivalent of TMEDA at the end of lithiation. d) ^{13}C NMR spectrum of 0.2 M $s\text{BuLi}$ in $[\text{D}_8]\text{THF}$ at 173 K with one equivalent of TMEDA. e) ^7Li NMR spectrum of 0.2 M **2** in $[\text{D}_8]\text{THF}$ at 173 K with one equivalent of TMEDA at the end of lithiation. An asterisk indicates an oxygen-derived impurity. Cy, b and s stand for cyclohexane, butane and starting styrene oxide, respectively. All spectra were measured at natural abundance lithium and carbon.

the ^{13}C (Figure 4b) and ^1H (Figure 5d) NMR spectra in the presence of both starting oxirane and “unreacted” $s\text{BuLi}$, the latter mainly present as a monomeric aggregate (vide supra). With time, the starting epoxide completely disappeared (Figures 4c, 5e). The new set of signals could be clearly ascribed to lithiated styrene oxide, either because several preparations were fully reproducible or because after “quenching” at low temperature with CH_3OD in the NMR tube the only species detected resulted to be α -deuterated styrene oxide (>98% D). As demonstrated by DEPT-135 (Figure 4c) and phase-sensitive heterocorrelation ^1H , ^{13}C -HSQC-DEPT experiments (Figure S9 in the Supporting Information), the signals in the range 163.0–119.0 ppm (δ = 162.4, 127.5, 122.2 and 119.7 ppm, Figure 4b,c) could only be assigned to the aromatic carbon atoms of lithiated styrene oxide; in the case of the *ortho*-, *para*- and *ipso*-

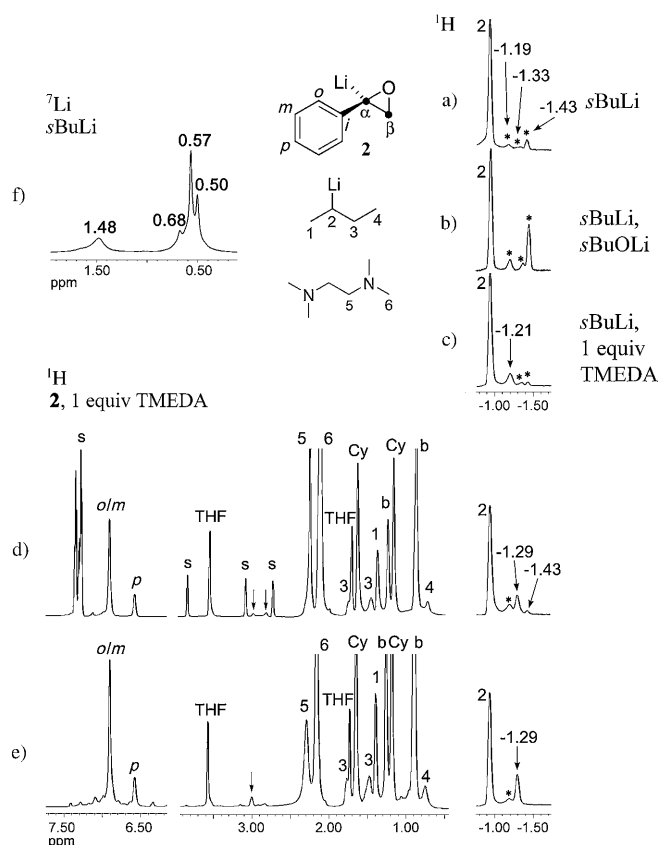


Figure 5. a) Partial ^1H NMR spectrum of 0.2 M $s\text{BuLi}$ in $[\text{D}_8]\text{THF}$ at 173 K. b) Partial ^1H NMR spectrum of 0.2 M $s\text{BuLi}/s\text{BuOLi}$ (0.5:1 O:Li ratio) in $[\text{D}_8]\text{THF}$ at 173 K. c) Partial ^1H NMR spectrum of 0.2 M $s\text{BuLi}$ in $[\text{D}_8]\text{THF}$ at 173 K with one equivalent of TMEDA. d) ^1H NMR spectrum of 0.2 M **2** in $[\text{D}_8]\text{THF}$ at 173 K with one equivalent of TMEDA at the beginning of lithiation. e) ^1H NMR spectrum of 0.2 M **2** in $[\text{D}_8]\text{THF}$ at 173 K with one equivalent of TMEDA at the end of lithiation. f) ^7Li NMR spectrum of 0.2 M $s\text{BuLi}$ in $[\text{D}_8]\text{THF}$ at 173 K. An asterisk indicates alkoxides/mixed aggregates with $s\text{BuLi}$. Cy, b and s stand for cyclohexane, butane and starting styrene oxide, respectively. All spectra were measured at natural abundance lithium and carbon.

carbon atoms, each signal showed also a shoulder. Moreover, the ^1H , ^{13}C -HSQC-DEPT spectrum showed that the two lowest field broad proton singlets at δ = 6.58 and 6.91 ppm (relative ratio 1:4, Figure 5d,e) correlate with only three cross-peaks with the corresponding aromatic carbon atoms (Figure S9 in the Supporting Information) so testifying an almost chemical shift isochronicity for *meta*- and *ortho*-aromatic protons. This finding is consistent with a ring rotation still fast on the NMR timescale at 173 K. The slight upfield shifts exhibited by *ortho*- and *para*-aromatic carbon atoms further to lithiation was in agreement with a negligible delocalisation of the π charge onto the phenyl ring, as suggested by DFT calculations (vide supra). In addition, the ^{13}C signal of the α -lithiated carbon appeared as a very broad singlet between 81.0–83.0 ppm not revealing any line splitting because of ^7Li coupling (Figure 4b).

At the earliest stage of deprotonation reaction, only two small broad oxiranyl CH peaks of the anion could be detect-

ed in the ^1H NMR spectrum at $\delta = 2.84$ and 3.00 ppm (Figure 5d). As the reaction progresses, other small peaks appeared between 6.00 and 7.50 ppm (aromatic region) flanking the main ones at $\delta = 6.58$ and 6.91 ppm as well as between 2.80 and 3.20 ppm (CH_2 region; Figure 5e). Similarly, the ^7Li NMR spectrum (Figure 4e) exhibited, besides a very broad signal centred at $\delta = 1.57$ ppm relative to $s\text{BuLi}$, up to seven peaks ($\delta = 0.01, 0.19, 0.50, 0.57, 0.61, 0.80$ and 1.32 ppm) representative of several nonequivalent lithium species; peaks at $\delta = 0.50$ and 0.57 ppm being most probably associated with alkoxides/mixed aggregates (vide infra and Figure 5f). These findings suggest that several differently aggregated species seem to coexist at this temperature and concentration in solution. The resonance of $\beta\text{-CH}_2$ oxiranyl carbon atom could only be indirectly detected by means of a $^1\text{H}, ^{13}\text{C}$ -HSQC-DEPT experiment, because it was hidden by the CH_2 groups of TMEDA at $\delta = 58.7$ ppm. In fact, this broad ^{13}C signal gave ^1H correlations with some CH_2 peaks present at the end of deprotonation reaction; in particular, with that at $\delta = 3.00$ ppm (Figure 5e and Figure S10 in the Supporting Information).^[36]

Running different experiments with 0.8 and 1.8 equivalents of $s\text{BuLi}$, the resulting spectra were identical (apart from additional signals deriving from excess neutral styrene oxide or excess organolithium), suggesting that no heteroaggregates between lithiated styrene oxide and organolithium occurred.^[37] Therefore, the “role” of $s\text{BuLi}$, coexisting with both the substrate and the lithiated epoxide throughout the deprotonation reaction, was investigated.

Formation of mixed alkoxides aggregates and organolithium-epoxide complexes: The ^1H NMR spectrum of 0.2M $s\text{BuLi}$ in $[\text{D}_8]\text{THF}$ at 173 K showed three more minor broad peaks shifted to higher field at $\delta = -1.19, -1.33$ and -1.43 (Figure 5a) in the region below 0 ppm (which is that corresponding to protons attached to the alkyllithium carbanionic carbon), apart from one main signal at -0.95 ppm, which was assigned to the proton attached to C-2 carbon of $s\text{BuLi}$ (from $^1\text{H}, ^{13}\text{C}$ -HSQC-DEPT shift correlation, Figure S8 in the Supporting Information). Similarly, ^7Li NMR spectrum showed in addition to the peak at $\delta = 1.48$ ppm corresponding to free $s\text{BuLi}$, three more peaks shifted to higher field at $\delta = 0.68, 0.57$ and 0.50 ppm (Figure 5f). As the presence of molecular oxygen in the solvent may lead to the formation of alkoxides, we wondered whether the aforementioned peaks might be due to mixed alkoxide complexes. Indeed, it has been reported that lithium alkoxides formed in less than stoichiometric amounts from alkyllithium compounds can produce mixed alkyllithium/lithium alkoxides aggregates.^[28b,38,39] To check the formation of possible mixed aggregates between $s\text{BuLi}$ and $s\text{BuOLi}$, the synthesis of $s\text{BuOLi}$ was accomplished by reacting a 0.2M solution of $s\text{BuLi}$ in THF with 2-butanol, the latter employed in less than stoichiometric amount ($0.5:1$ O/Li ratio). The ^1H NMR spectrum for this sample contained the same peaks seen in the 0.2M solution of $s\text{BuLi}$ in THF (that is, at $\delta = -0.95, -1.19, -1.33$ and -1.43 ppm), although with slightly different in-

tensities (Figure 5b). However, no further attempts were made to elucidate the solution structure of the above aggregates.^[40] Running a ^{13}C NMR spectrum of a $1:1$ mixture $s\text{BuLi}/\text{TMEDA}$ in THF (0.2M), the TMEDA CH_2 resonance fell to $\delta = 58.1$ ppm at 173 K (Figure 4d) and in the ^1H NMR spectrum a new broad singlet appeared below 0 at -1.21 ppm flanking the main one at -0.95 corresponding to “free” $s\text{BuLi}$ (Figure 5c). The new upfield shift of the $s\text{BuLi}$ α -methine proton may be the consequence of an increase of the negative charge on the carbanion, because of the complexation of the lithium by the diamine, as similarly reported.^[41] Therefore, it seems as though a low TMEDA concentration is able to compete with bulk THF for coordination sites on lithium of $s\text{BuLi}$. Once styrene oxide starts to be deprotonated with such a $1:1$ mixture $s\text{BuLi}/\text{TMEDA}$ in THF, as the lithiation progresses, the TMEDA CH_2 resonance broadens considerably and moves downfield by about 0.5 ppm to $\delta = 58.7$ ppm (Figure 4b). In the ^1H NMR spectrum, a new broad peak shifted to higher field forms at $\delta = -1.29$ ppm at the expense of the previous one at $\delta = -1.21$ ppm, the former being also flanked by two small and broad peaks at $\delta = -1.19$ and -1.43 ppm (Figure 5d). At the end of the deprotonation reaction, in the ^{13}C NMR spectrum, the TMEDA CH_2 resonance once again moves upfield to $\delta = 58.1$ ppm (Figure 4c) and, in the ^1H NMR spectrum, the peak at $\delta = -1.29$ ppm increases its intensity, whereas that at $\delta = -1.43$ ppm disappears (Figure 5e). The above scenario always recurs each time styrene oxide is deprotonated with an excess $s\text{BuLi}$ in the presence of TMEDA. However, it was not established whether the disappearance of the peak at $\delta = -1.43$ ppm was due to a competitive reaction of one of the $s\text{BuLi}/s\text{BuOLi}$ aggregates with the epoxide or rather to the slow and reversible formation of an epoxide-alkyllithium complex, which undergoes deprotonation. Most likely, the peak at $\delta = -1.29$ ppm, the intensity of which increases with time, may be related to the complex between lithiated epoxide and $s\text{BuLi}$; in fact, performing the lithiation with a sub-stoichiometric amount of $s\text{BuLi}$ in the presence of TMEDA both the peaks at $\delta = -0.95$ and -1.29 ppm are absent. On the other hand, the broadening and the shifting that the TMEDA CH_2 resonance undergoes during the course of lithiation supports the hypothesis that a dynamic exchange between the complex $s\text{BuLi}/\text{TMEDA}$ with both neutral and lithiated styrene oxide may be really underway. NMR studies of organolithium-epoxide complexes reported in the literature^[42] have provided evidence for the tendency of epoxide oxygen atom to lithium coordination. That a complex-induced proximity effect (CIPE)^[43a-d] may be playing a role in the course of lithiation of styrene oxide seems reasonable, also considering the competition occurring between α - and β -deprotonation (vide infra). Recently, the regioselective (α - vs. *ortho*) lithiation of *N*-alkylarylaziridines has similarly been rationalised on the basis of a CIPE effect, which would operate jointly with stereodynamics occurring at the aziridine nitrogen.^[43e] To date, such pre-lithiation complexes have been barely observed spectroscopically.^[44] To get more information about

the solution structure of this lithiated epoxide, we synthesised a doubly ^{13}C -enriched styrene oxide on the epoxide ring.

^{13}C , ^1H , ^7Li and ^6Li NMR spectroscopic studies—deprotonation of $[\alpha,\beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$

^{13}C NMR investigation in $[\text{D}_8]\text{THF}$ at 173 K: $[\alpha,\beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$ was synthesised in 76 % yield by epoxidation of the corresponding $[\alpha,\beta\text{-}^{13}\text{C}_2]\text{styrene}$ (see Experimental Section). When a mixture of one equivalent of this doubly ^{13}C enriched epoxide and one equivalent of TMEDA in $[\text{D}_8]\text{THF}$ was treated at 173 K with 0.8 equivalents of $s\text{BuLi}$ (0.2 M being the resulting solution), new sets of signals in the range 57.0–93.0 ppm were now clearly detected in the ^{13}C NMR spectrum (Figure 6). DEPT-135 analysis revealed

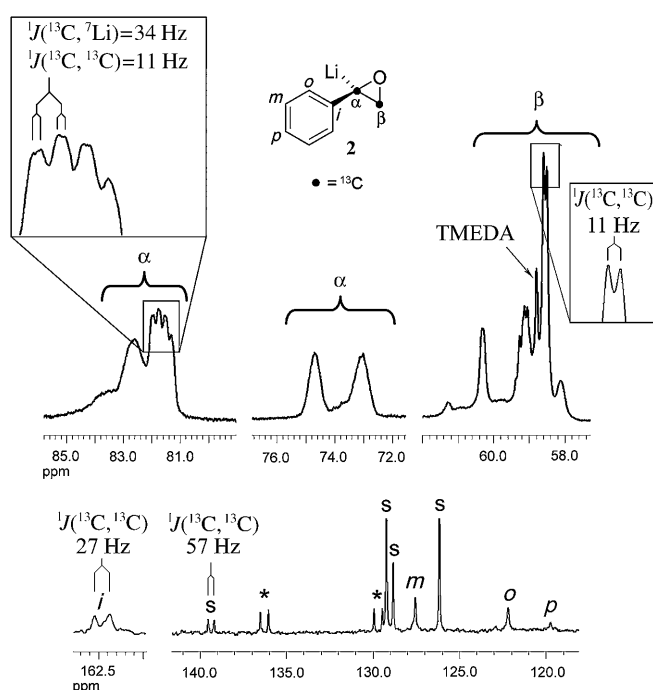


Figure 6. ^{13}C NMR spectrum of 0.2 M lithiated $[\alpha,\beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$ in $[\text{D}_8]\text{THF}$ at 173 K with one equivalent of TMEDA. s and o, m, p stand for starting $[\alpha,\beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$ and *ortho*-, *meta*- and *para*-carbon atoms of lithiated $[\alpha,\beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$, respectively. An asterisk indicates a CH vinylic carbon.

the presence of at least four chemically nonequivalent CH_2 groups ($\delta = 58.1, 58.5, 59.1$, and 60.3 ppm), one CH signal at $\delta = 61.2$ ppm, six broad signals assignable to quaternary carbon atoms ($\delta = 73.1, 73.7, 74.7, 81.6, 82.6$, and 83.7 ppm) and another small CH peak at $\delta = 92.6$ ppm (vide infra). Above all, most diagnostic was the signal at $\delta = 81.6$ ppm, which exhibited a broad 1:1:1:1 quartet (^7Li $I = 3/2$) typical of a carbon coupled to only one lithium atom ($J(^{13}\text{C}, ^7\text{Li}) = 34$ Hz), each line being further poorly split into a doublet because of a $^{13}\text{C}, ^{13}\text{C}$ coupling ($J(^{13}\text{C}, ^{13}\text{C}) = 11$ Hz; Figure 6); it may be presumably indicating the presence in the reaction

mixture of a monomeric contact ion pair (CIP). The complementary $^{13}\text{C}, ^{13}\text{C}$ coupling constant value was found for the CH_2 signal at $\delta = 58.6$ ppm ($J(^{13}\text{C}, ^{13}\text{C}) = 11$ Hz). This fact is consistent with a close connection of the above carbon atoms within the same aggregate. In nonlithiated doubly ^{13}C -enriched styrene oxide the $^{13}\text{C}, ^{13}\text{C}$ coupling constant value between the two oxirane-ring carbon atoms is 28 Hz; therefore, there has been a decrease in the constant further to lithiation ($\Delta J(^{13}\text{C}, ^{13}\text{C}) = -17$ Hz). Similarly, the $^{13}\text{C}, ^{13}\text{C}$ coupling constant between the *ipso* and the α -carbon also decreased on lithiation from 57 to 27 Hz (Figure 6).

An analogous trend was found by Seebach^[45] in some lithiated organohalides for the coupling constants between carbenoid C atoms and ^{13}C nuclei directly attached to them; this fact has been interpreted as the consequence of a reduced degree of hybridisation of such lithiated carbon atoms.

Over the range 119–140 ppm, two doublets associated with two CH carbon atoms (from DEPT-135 analysis), strongly coupled to each other by means of their ^{13}C nuclei ($J(^{13}\text{C}, ^{13}\text{C}) = 72$ Hz), were noted at $\delta = 129.7$ and 136.2 ppm (Figure 6). They were assigned to the two vinylic CH carbon atoms of the *trans*-alkene 3-methyl-1-phenyl-pent-1-ene **5** (Figure 7).^[46] This kind of alkene was previously observed

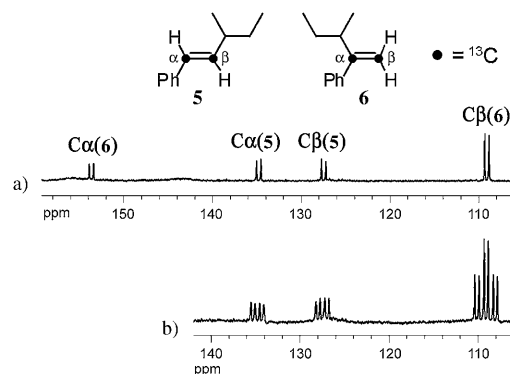


Figure 7. a) and b) refer to $^{13}\text{C}\{^1\text{H}\}$ and $^1\text{H}\text{-}^{13}\text{C}$ full-coupled NMR spectra, respectively, of 0.2 M lithiated $[\alpha,\beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$ in $[\text{D}_8]\text{THF}$ with one equivalent of TMEDA after warming up to room temperature from 173 K.

by our group studying the “alkylative reduction” of lithiated styrene oxide promoted by $s\text{BuLi}$ ^[14] and by Mioskowski (see also Scheme 8).^[47,48] Interestingly, by warming up a solution of such an anion in the presence of an excess $s\text{BuLi}$ suddenly to room temperature, another pair of two doublets flanking the previous ones appeared at $\delta = 153.7$ and 109.1 ppm ($J(^{13}\text{C}, ^{13}\text{C}) = 72$ Hz, Figure 7 a). The corresponding $^1\text{H}, ^{13}\text{C}$ fully coupled spectrum (Figure 7 b) revealed that they correspond to two vinylic carbon atoms: a quaternary carbon ($\delta = 153.7$ ppm, d, $J(^{13}\text{C}, ^{13}\text{C}) = 72$ Hz) and a CH_2 carbon ($\delta = 109.1$ ppm, td, $J(^{13}\text{C}, ^1\text{H}) = 156$ Hz, $J(^{13}\text{C}, ^{13}\text{C}) = 72$ Hz); they were assigned to the alkene 3-methyl-2-phenyl-pent-1-ene (**6**; Figure 7, see also Scheme 8).^[14,47] A 2D $^{13}\text{C}, ^{13}\text{C}$ COSY experiment confirmed that the two pairs of doublets

refer to ^{13}C nuclei scalar coupled to each other within two different alkenes (Figure S11 in the Supporting Information). The above regioisomeric alkenes may derive from a stereospecific intermolecular alkylative insertion into C–Li bonds of the corresponding carbenoid intermediates further to both α - and β -proton abstraction promoted by *s*BuLi, as reported^[47] (vide infra).

Interaction with TMEDA: A 0.2 M sample of **2** without TMEDA was prepared and a $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum was run at 173 K in $[\text{D}_8]\text{THF}$. A broad 1:1:1:1 quartet ($^1J(^{13}\text{C}, ^7\text{Li}) = 34$ Hz) centred at $\delta = 81.2$ ppm and with a fine structure again appeared (Figure 8a). It was flanked on both sides by three other broad peaks at $\delta = 81.8$, 83.2 and 83.8 ppm and at $\delta = 73.0$, 73.6 and 74.7 ppm, all corresponding to quaternary carbon atoms. The CH_2 region (57.0–61.0 ppm) consisted of a doublet ($^1J(^{13}\text{C}, ^{13}\text{C}) = 11$ Hz) at $\delta = 58.6$ ppm with a shoulder on the right side, two overlapping broad doublets at $\delta = 58.8$ and 58.9 ppm ($^1J(^{13}\text{C}, ^{13}\text{C})$ ca. 11 Hz), the latter with a shoulder on the left side ($\delta =$

59.2 ppm), and another broad singlet at $\delta = 60.3$ ppm. A triple-resonance experiment, $^{13}\text{C}\{^1\text{H}, ^7\text{Li}\}$, was run on the same sample; the residual coupling constants still present in the spectrum for the various peaks now being referable to $^{13}\text{C}, ^{13}\text{C}$ couplings only (Figure 8d). Under this double decoupling, the previous broad quartet at $\delta = 81.2$ ppm became a narrow doublet ($^1J(^{13}\text{C}, ^{13}\text{C}) = 11$ Hz), the broad peak at $\delta = 81.8$ ppm resolved into two doublets of equal intensity at $\delta = 81.6$ and 82.0 ppm (each one with a $^1J(^{13}\text{C}, ^{13}\text{C}) = 11$ Hz) and, as a shoulder of the latter doublet, two more doublets ($^1J(^{13}\text{C}, ^{13}\text{C})$ ca. 13 Hz) at $\delta = 82.2$ and 82.5 ppm were also observed (see inset in Figure 8d).

Moreover, the broad peak at $\delta = 74.7$ ppm (Figure 8a) now exhibits a fine structure with at least four $^{13}\text{C}, ^{13}\text{C}$ couplings ($^1J(^{13}\text{C}, ^{13}\text{C}) = 12$ Hz) (see inset in Figure 8d), and the line widths of the peaks at $\delta = 73.0$, 73.6, 83.2 and 83.8 reduced as a possible consequence of a missing $^{13}\text{C}, ^7\text{Li}$ coupling after ^7Li decoupling. Homonuclear shift correlations within a $^{13}\text{C}, ^{13}\text{C}$ COSY spectrum (see Figure S12 in the Supporting Information) together with concentration-dependent

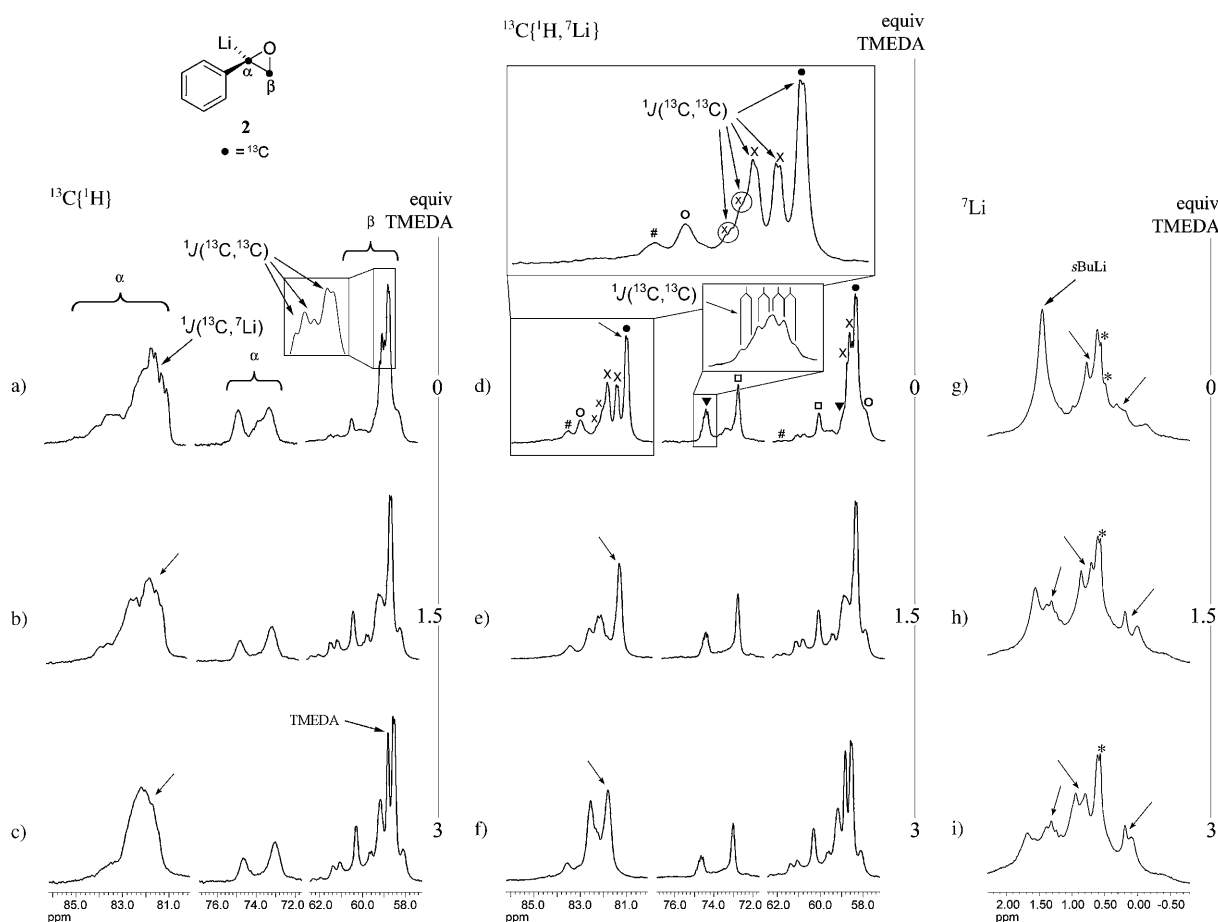
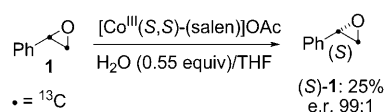


Figure 8. a), b) and c) refer to $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of 0.2 M lithiated $[\alpha, \beta\text{-}^{13}\text{C}_2]$ styrene oxide in $[\text{D}_8]\text{THF}$ at 173 K without TMEDA and after addition of 1.5 and 3 equivalents, respectively. d), e) and f) refer to $^{13}\text{C}\{^1\text{H}, ^7\text{Li}\}$ NMR spectra of 0.2 M lithiated $[\alpha, \beta\text{-}^{13}\text{C}_2]$ styrene oxide in $[\text{D}_8]\text{THF}$ at 173 K without TMEDA and after addition of 1.5 and 3 equivalents, respectively. g), h) and i) refer to ^7Li NMR spectra of 0.2 M lithiated $[\alpha, \beta\text{-}^{13}\text{C}_2]$ styrene oxide in $[\text{D}_8]\text{THF}$ at 173 K without TMEDA and after addition of 1.5 and 3 equivalents, respectively. Similar symbols in Figure 8d refer to quaternary and CH_2 carbon atoms within a certain aggregate, as described in the legend. An asterisk in g)–i) indicates alkoxides/mixed aggregates with *s*BuLi. Legend: ■ monomer; ×, ○, # stereoisomeric dimers; □ bridged dimer; ▼ tetramer; * alkoxides/mixed aggregates with *s*BuLi.

studies and warming experiments, that favoured the anion decomposition (vide infra), allowed us to match all the quaternary carbon atoms with the corresponding CH₂ groups as shown in Figure 8d.^[49] The above results were always reproducible. Upon addition of TMEDA (up to 3 equiv), a slight downfield shift of the signal representative of the carbanionic carbon at $\delta=81.2$ ppm took place ($\Delta\delta=0.3$ and 0.6 ppm with 1 and 3 equiv of TMEDA, respectively), particularly noticeable in the corresponding ¹³C{¹H,⁷Li} spectra (Figure 8e,f). The formation of a different type of ion pair differing in the degree of (lithium) solvation seems implausible as the coupling with lithium was always preserved (Figure 8b,c). A solvent-separated ion pair (SSIP), for example, would give rise to a rather drastic change in both the ¹H and ¹³C NMR spectra of the anion **2**.^[50] In the ¹H NMR spectrum, two main sets of aromatic protons (at $\delta=6.58$ and 6.91 ppm, of the same kind of those depicted in Figure 5d,e) continued to be present without any change in their chemical shifts. We therefore assigned the carbanionic carbon peak moving at higher δ values to the TMEDA-solvated monomer, in which just a slight lengthening of the C–Li bond may take place. Similarly, in the case of aryllithium reagents, monomeric TMEDA complexes have shown a very high lability to ligand exchange.^[51] It has been reported that the relative affinities of TMEDA and THF for lithium may be highly substrate-dependent.^[52] On the basis of the above results, we conclude that TMEDA competes with bulk THF for coordination sites on lithium at least relatively to the η^1 -monomeric aggregate. As far as the signals in the range 81.0–83.0 ppm are concerned, they tended to merge in a major one as the amount of TMEDA increased (Figure 8b,c and 8e,f), whereas those falling at $\delta=73.0$ and 74.7 ppm were not influenced at all by added TMEDA. This co-solvent, however, favoured the peak at $\delta=73.6$ ppm to be coalesced with that at $\delta=73.0$ ppm, the intensity of which also increased (Figure 8b,c and 8e,f). ⁷Li NMR spectra revealed that the signal at $\delta=0.79$ ppm (Figure 8g) was, as a matter of fact, a broad doublet centred at $\delta=0.71$ ppm (¹J(¹³C,⁷Li)=34 Hz). In fact, it gradually moved downfield in the range 0.6–1.0 ppm as more TMEDA was added, similar to the signal of the carbanionic carbon of the monomeric aggregate (Figure 8h,i); therefore, they are related. Moreover, in ⁷Li NMR spectra, addition up to three equivalents of TMEDA also promoted a dynamic exchange and partial coalescence of the very broad signals in the range –0.5–0.4 ppm (peaks at $\delta=-0.48$, –0.11, 0.20, 0.32 ppm, Figure 8h,i) similar to that observed in the ¹³C NMR spectra (range 81.0–83.0 ppm, Figure 8e,f). Finally, as *s*BuLi reacted, three more overlapping peaks at $\delta=1.24$, 1.32 and 1.38 ppm were noted in ⁷Li NMR spectra (Figure 8h,i) reminiscent of a broad 1:2:1 triplet (¹J(¹³C,⁷Li) ca. 16 Hz), which would be suggestive of a lithium bonded to two ¹³C chemically equivalent nuclei and the chemical shift of which did not change during TMEDA titration (vide infra). Now, the question is what about the nature of these several aggregates coexisting in solution in slow equilibrium with the monomer?

Hydrolytic kinetic resolution and deprotonation: DFT calculations suggested that in a fully-equilibrated solution of lithiated styrene oxide in THF, a monomeric species such as [**2a**-(thf)₃] might be in equilibrium with a mixture of four THF-solvated dimers, such as [**4a**(thf)₂]-[**4d**(thf)₂], which are close in energy. As NMR spectra may be actually more complicated than expected, owing to the possible presence in solution of multiple stereoisomers for each aggregate because of epoxide chirality, we decided to synthesise a doubly ¹³C-enriched styrene oxide (enantiomerically enriched) in order to investigate this aspect. The hydrolytic kinetic resolution of [α,β -¹³C₂]styrene oxide catalysed by [Co^{III}(*S,S*)-(salen)]OAc complex^[53] furnished the chiral nonracemic (*S*)-[α,β -¹³C₂]styrene oxide **1** (25 %, e.r. 99:1; see Experimental Section; Scheme 3).



Scheme 3. Hydrolytic kinetic resolution of [α,β -¹³C₂]styrene oxide **1**.

A 0.15 M sample of the above optically active epoxide in [D₈]THF was treated with 1.2 equivalents of *s*BuLi in the absence of TMEDA and a ¹³C{¹H,⁷Li} NMR spectrum was run at 173 K. Because lithiated styrene oxide is known to be configurationally stable, having employed a chiral nonracemic substrate, only homochiral aggregates are expected to form. Compared to the ¹³C NMR spectrum shown in Figure 8d, which refers to the deprotonation of a racemic substrate, it is now worth noting the disappearance of only the broad peak at $\delta=83.2$ ppm over the range 80.0–85.0 ppm (Figure 9a).

In addition, over the range 72.0–76.0 ppm there was, apparently, just a spectral simplification in between the two main broad peaks at $\delta=73.0$ and 74.7 ppm (Figure 9a). The ⁷Li NMR spectrum (Figure 9c) consisted of sets of signals similar to those depicted in Figure 8g. The acquisition of ⁷Li spectra under simultaneous ¹³C decoupling proved to be crucial in confirming the presence of a doublet at $\delta=0.71$ ppm (Figure 9d) and a triplet at $\delta=1.32$ ppm; indeed, the latter collapsed to give a singlet. However, this was visible only after diluting the sample (0.075 M) owing to the tail of *s*BuLi (vide infra; compare also Figure 8i with Figure 9f).

⁷Li,¹³C shift correlation: To assign and correlate the various ⁷Li resonances to the ¹³C nuclei of the several equilibrating aggregates present in solution, a ⁷Li,¹³C heteronuclear multiple quantum correlation (HMQC) experiment was set up (Figure 10). In contrast with ⁶Li,¹³C shift correlation, which is a well-established NMR technique,^[54] to the best of our knowledge this type of experiment has never been described before.^[55]

When a delay $\Delta_2=1/2J$ of 16.7 ms for the preparation of *anti*-phase magnetisation was used, the connectivity between the ⁷Li,¹³C spin pairs showed a correlation between the ¹³C

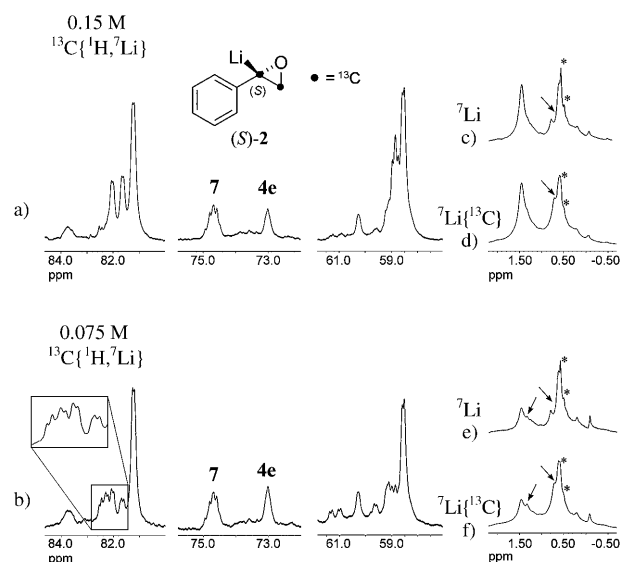


Figure 9. a) $^{13}\text{C}\{^1\text{H},^7\text{Li}\}$ NMR spectrum of 0.15 M lithiated (S)-[$\alpha,\beta\text{-}^{13}\text{C}_2$]styrene oxide in $[\text{D}_8]\text{THF}$ at 173 K. b) $^{13}\text{C}\{^1\text{H},^7\text{Li}\}$ NMR spectrum of 0.075 M lithiated (S)-[$\alpha,\beta\text{-}^{13}\text{C}_2$]styrene oxide in $[\text{D}_8]\text{THF}$ at 173 K. c) and d) refer to ^7Li NMR spectra of 0.15 M lithiated (S)-[$\alpha,\beta\text{-}^{13}\text{C}_2$]styrene oxide in $[\text{D}_8]\text{THF}$ at 173 K acquired without and under ^{13}C decoupling, respectively. e) and f) refer to ^7Li NMR spectra of 0.075 M lithiated (S)-[$\alpha,\beta\text{-}^{13}\text{C}_2$]styrene oxide in $[\text{D}_8]\text{THF}$ at 173 K acquired without and under ^{13}C decoupling, respectively. An asterisk in c)–f) indicates alkoxides/mixed aggregates with *s*BuLi. **4e** and **7** refer to tetrameric and four-centre dimeric structures, respectively (see Scheme 4 and the body text).

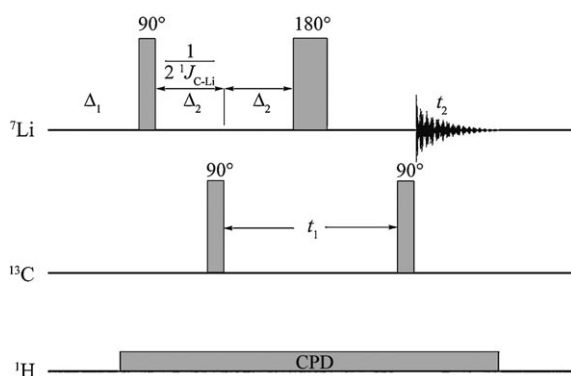


Figure 10. Pulse sequence of $^7\text{Li},^{13}\text{C}\{^1\text{H}\}$ HMQC spectrum without ^{13}C decoupling during acquisition.

signal at $\delta=81.2$ ppm with a lithium doublet ($(^{13}\text{C},^7\text{Li})=34$ Hz) at $\delta=0.72$ ppm; a multiplicity that is consistent with a lithium bound to only one carbon atom (Figure 11).

In addition, this type of experiment disclosed another interesting correlation between the multiplet at $\delta=73.0$ ppm in the ^{13}C spectrum (usually unresolved) and a broad lithium triplet (reminiscent of 1:2:1 intensities) ($J(^{13}\text{C},^7\text{Li})=16$ Hz) at $\delta=1.32$ ppm, which is consistent with a lithium bound to two chemically equivalent ^{13}C carbon atoms. In the ^7Li spectrum this broad triplet is usually covered by the tail of *s*BuLi when an excess of base is used (Figure 8 g–i). A plau-

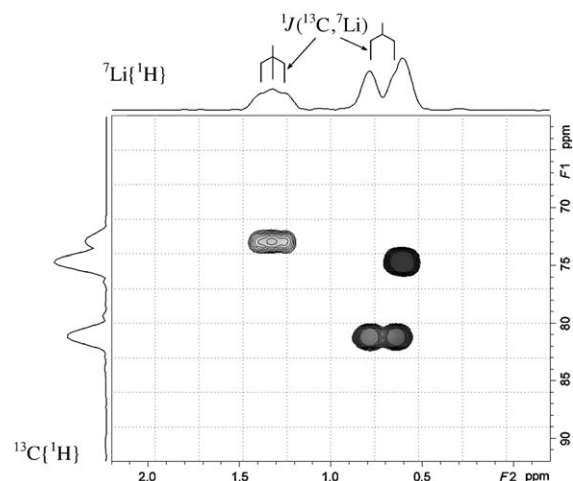
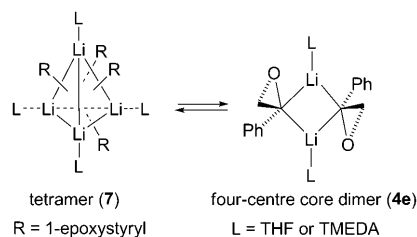


Figure 11. $^7\text{Li},^{13}\text{C}\{^1\text{H}\}$ HMQC spectrum of 0.15 M lithiated (S)-[$\alpha,\beta\text{-}^{13}\text{C}_2$]styrene oxide in $[\text{D}_8]\text{THF}$ at 173 K, pulse sequence of Figure 10, $\Delta_2=16.7$ ms, experimental time 19.22 min.

sible explanation is that a four-centre homochiral dimeric structure with coordination only to carbon (**4e**; Scheme 4) may also be present in equilibrium in the reaction mixture. Another correlation was established between the multiplet at $\delta=74.7$ ppm (^{13}C spectrum) and the broad ^7Li signal at $\delta=0.60$ ppm (Figure 11).



Scheme 4. A four-centre dimeric structure (**4e**) in equilibrium with a tetrameric aggregate (**7**).

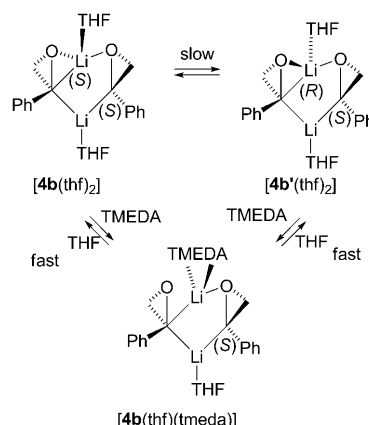
Interestingly, this last connectivity was the only one seen in the $^7\text{Li},^{13}\text{C}$ HMQC spectrum when a delay $\Delta_2=50$ ms, optimised for a $^1J(^{13}\text{C},^7\text{Li})=10$ Hz, was used (see Figure S13 in the Supporting Information). This smaller J value at which the above peak showed its highest intensity is suggestive of the presence in solution of a higher aggregate, such as a fluxional tetramer (**7**; Scheme 4; vide infra).^[35] Not unexpectedly, the broadest lithium signals seen midway through -0.50 to 0.40 ppm (Figure 9c) did not show any ^{13}C correlation, most probably because the transverse magnetisation generated at the beginning of the pulse sequence (associated to a fast transverse relaxation) was completely lost during the delays involved in the experiment.^[56]

Therefore, lithium peaks falling in the above range (-0.50 to 0.40 ppm) (Figure 9c) were tentatively assigned to the carbon atoms present over the range $81.5\text{--}84.0$ ppm as, similarly to these carbon signals, the former experienced dynamic effects in the presence of TMEDA. Lithium peaks at $\delta=$

0.50 and 0.57 ppm (Figure 9c) were associated to alkoxides/mixed aggregates (see Figure 5 f).^[57]

Concentration-dependent studies: The above NMR sample (0.15 M) was then diluted with $[D_8]THF$ (0.5 mL) in order to obtain a 0.075 M solution and run again at 173 K. Dilution, in principle, should break down higher aggregates into smaller ones. Indeed, relative amount of the various species present in the reaction mixture exhibited a dependence on the total concentration in oxiranyllithium (Figure 9b). In particular, over the range 81.0–84.0 ppm, the two doublets at $\delta = 81.6$ and 82.0 ppm underwent a strong decrease in their intensity with respect to the peak at $\delta = 81.2$ ppm, assigned to the THF-solvated monomer (Figure 9b). Two pairs of doublets are now clearly visible (see inset in Figure 9b); the intensities of the more downfield-shifted ones (peaks at $\delta = 82.5$, 82.2 ppm) together with that of the broad peak at $\delta = 83.7$ ppm do not change much. On the other hand, the relative concentrations of species **4e** and **7** (Figure 9a,b and Scheme 4) changed after dilution, as was observed in the change of intensity for the signals in the range 72.5–75.0 ppm, that of **4e** rising apparently at the expense of that for **7**, the intensity of which decreased instead. This means that **7** should be more aggregate than **4e**. These last two species, namely **4e** and **7**, could in principle be quantitated at 173 K as their signals are well resolved. However, a plot of $\log[7]$ vs $\log[4e]$ showed a slope of 1.40.^[58] An equilibrium between a dimer and a trimer seems unlikely as cyclic trimers of organolithium compounds are very rare and, to our knowledge, have never been observed in polar solvents such as THF.^[59] Taking also into account indications arising from $^{13}C, ^7Li$ shift correlations, we interpret the above deviation in terms of a slow equilibration on the NMR time-scale between a fluxional tetramer and a four-centre dimer, both being homochiral (Scheme 4).^[60] Then, we tried to interpret signals that relate to quaternary lithiated carbon atoms between 80.0–85.0 ppm in ^{13}C NMR spectrum which did not give any 7Li correlation in 2D HMQC spectrum.

Lithium as a centre of chirality: Among the four THF-solvated dimers ($[4a(thf)_2]$ – $[4d(thf)_2]$) (predicted by calculations to be in equilibrium with the monomer $[2a(thf)_3]$), the two candidate homochiral dimers to be taken into consideration when using a doubly ^{13}C -enriched and optically active styrene oxide would be $[4b(thf)_2]$ and $[4c(thf)_2]$. The solvated dimer $[4b(thf)_2]$, in particular, has been shown to change its structural features, owing to partial breaking of some C_α –Li bonds. In this situation, there would be a partial destruction of the molecular symmetry as one of the two lithium atoms becomes a centre of chirality. Therefore, two diastereomers ($[4b(thf)_2]$ and $[4b'(thf)_2]$; Scheme 5) are expected to form, each one exhibiting a pair of diastereotopic lithiated carbon atoms. In this view, one possible interpretation of the two pairs of doublets seen midway 80.0–85.0 ppm may be that they would be just related to two pairs of diastereotopic lithiated carbon atoms within two diastereomeric dimeric aggregates both having partially closed C–Li bonds



Scheme 5. Proposed mechanism for the interconversion of diastereoisomer $[4b(thf)_2]$ into $[4b'(thf)_2]$ through $[4b(thf)(tmeda)]$.

and being also under slow equilibration on the NMR time-scale (Scheme 5).^[61]

On the basis of the above assumption, we tentatively assigned the broad signal at $\delta = 83.8$ ppm to the other homochiral bridged dimer, that is $[4c(thf)_2]$; it could be similarly affected by such a dynamics because of the broadness of its linewidth. On the other hand, the signal disappearing at $\delta = 83.2$ ppm after employing chiral nonracemic styrene oxide may correspond to a possible heterochiral dimer such as $[4a(thf)_2]$ or $[4d(thf)_2]$. Inversion at lithium, which would favour the interconversion between diastereomers $[4b(thf)_2]$ and $[4b'(thf)_2]$, may occur after a decoordination of one of the two oxirane oxygen atoms or, alternatively, THF desolvation. This interpretation would also give a rationale to the coalescence observed in the presence of TMEDA over the range 80.0–85.0 ppm (Figure 8b,c,e,f). TMEDA, in fact, may promote for a dimer such as $[4b(thf)_2]$ a faster exchange between the two diastereomeric aggregates $[4b(thf)_2]$ and $[4b'(thf)_2]$ through $[4b(thf)(tmeda)]$ just competing with THF for coordination sites on lithium (Scheme 5). Unfortunately, we were not able to calculate the lithium inversion barrier because of the anion decomposition at a higher temperature than 173 K (vide infra).

C–O and C–Li bonds in α -lithiated ethers: α -Lithiated ethers are known to be carbenoid species with elongated C–O bond lengths between the anionic carbon and the oxygen atoms relative to the C–O bond lengths in the corresponding non-lithiated species. The higher the electrophilic character, the more elongated the carbenoid C–O bonds and the larger the downfield shift of the carbenoid ^{13}C atom.^[7b–d,11] However, that a dimeric organolithium compound, deriving from organic ring systems containing a heteroatom (e.g., N, O, S), may exhibit a solution structure different from that of “classic” bridged dimers (in which two bridging organic group participate in three-centre two-electron bonds) has precedent in the literature.^[62] In view of this, the fine structure exhibited by the peak at $\delta = 74.7$ ppm (assigned to a homochiral tetrameric aggregate), and observed only after run-

ning a $^{13}\text{C}\{^1\text{H}, ^7\text{Li}\}$ NMR spectrum (Figure 8d), may be tentatively interpreted in terms of four overlapping doublets owing to $^{13}\text{C}, ^{13}\text{C}$ couplings ($^1J(^{13}\text{C}, ^{13}\text{C}) \approx 12$ Hz), each one representative of a diastereotopic and therefore unisochronous carbanion carbon atom making up part of a nonsymmetric C_4Li_4 tetrameric core, most probably again owing to possible different intradimer $\text{C}_\alpha\text{-Li}$ and/or Li-O bond types present.^[63, 64]

In an attempt to shed more light on the “nature” and the structure of the various aggregation states of lithiated styrene oxide in solution, we ran other experiments this time employing $s\text{Bu}^7\text{Li}$ as the base. In fact, the faster ^7Li quadrupole relaxation generally leads to line broadening and thereby masking line splitting, whereas scalar spin–spin J couplings to neighbouring nuclei could be better resolved in the case of ^6Li , because of the favourable properties of this isotope ($I=1$, very small quadrupole moment).

^{13}C , ^1H , ^7Li and ^6Li NMR spectroscopic studies— $[\alpha, \beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$: lithiation with $s\text{Bu}^6\text{Li}$

^{13}C NMR investigation in $[\text{D}_8]\text{THF}$ at 173 K: $s\text{Bu}^6\text{Li}$ (96 % enrichment) was more conveniently prepared, with respect to the reported experimental procedure which makes use of ^6Li dispersion (5 % Na) in pentane,^[65] from ^6Li and 2-chlorobutane under sonic waves as in the case of $n\text{Bu}^6\text{Li}$ (see Experimental Section).^[66] A sample of $[\alpha, \beta\text{-}^{13}\text{C}_2]\text{oxiranyllithium}$ (**2**) in $[\text{D}_8]\text{THF}$ (0.3 M, prepared by treatment 1 equiv of styrene oxide with 1.2 equiv of $s\text{Bu}^6\text{Li}$) was run at 173 K without TMEDA. The resulting ^{13}C NMR spectrum (Figure 12) was very similar to the one obtained by using $s\text{Bu}^7\text{Li}$ in absence of TMEDA (0.2 M), but run as $^{13}\text{C}\{^1\text{H}, ^7\text{Li}\}$ (Figure 8d). The “apparent quartet” centred at $\delta = 81.2$ ppm may be interpreted as the result of the split of a triplet [because of $^{13}\text{C}, ^6\text{Li}$ coupling ($^1J(^{13}\text{C}, ^6\text{Li}) = 12$ Hz)] into three overlapping

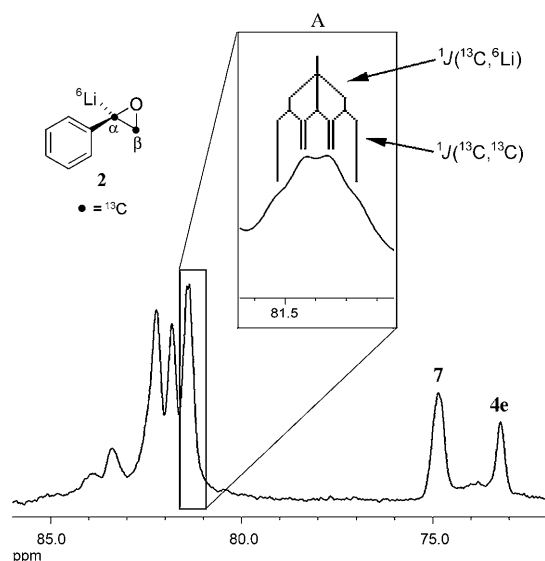


Figure 12. ^{13}C NMR spectrum of 0.3 M lithiated $[\alpha, \beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$ in $[\text{D}_8]\text{THF}$ at 173 K obtained using $s\text{Bu}^6\text{Li}$ in absence of TMEDA.

doublets [because of $^{13}\text{C}, ^{13}\text{C}$ coupling ($^1J(^{13}\text{C}, ^{13}\text{C}) = 11$ Hz)], the value of the former coupling constant lying again within the typical range of monomeric species. Unfortunately, the signals of the other carbanionic carbon atoms, falling either down- or upfield with respect to that of the monomeric aggregate, continued to appear as broad singlets. Most likely, for a coupling constant value $^1J(^{13}\text{C}, ^6\text{Li})$ lower than 12 Hz (as one would be expected for higher aggregates)^[35] the co-presence of a small (11 Hz) $^{13}\text{C}, ^{13}\text{C}$ coupling constant allows both couplings to merge into unresolved peaks.

Effect of temperature: Effect of temperature on the thermal stability of α -lithiated styrene oxide has also been investigated. A 0.2 M sample of $[\alpha, \beta\text{-}^{13}\text{C}_2]\text{oxiranyllithium}$ (**2**), prepared using one equivalent of $s\text{Bu}^6\text{Li}$ and three equivalents of TMEDA, was gently warmed from 173 to 232 K: four new pairs of doublets, each one corresponding to a C–H carbon (as confirmed by a DEPT-135 analysis), formed in the corresponding ^{13}C NMR spectrum (Figure 13c) in addition to those discussed above (Figure 7a): two doublets centred at $\delta = 101.3$ ($^1J(^{13}\text{C}, ^{13}\text{C}) = 78$ Hz) and 102.3 ppm ($^1J(^{13}\text{C}, ^{13}\text{C}) = 78$ Hz), the other two at $\delta = 158.4$ ($^1J(^{13}\text{C}, ^{13}\text{C}) = 78$ Hz) and 159.5 ppm ($^1J(^{13}\text{C}, ^{13}\text{C}) = 78$ Hz). By quenching of the reaction mixture with CH_3OH , one of the main byproducts detected by ^1H NMR spectroscopy and GC-MS analysis in the

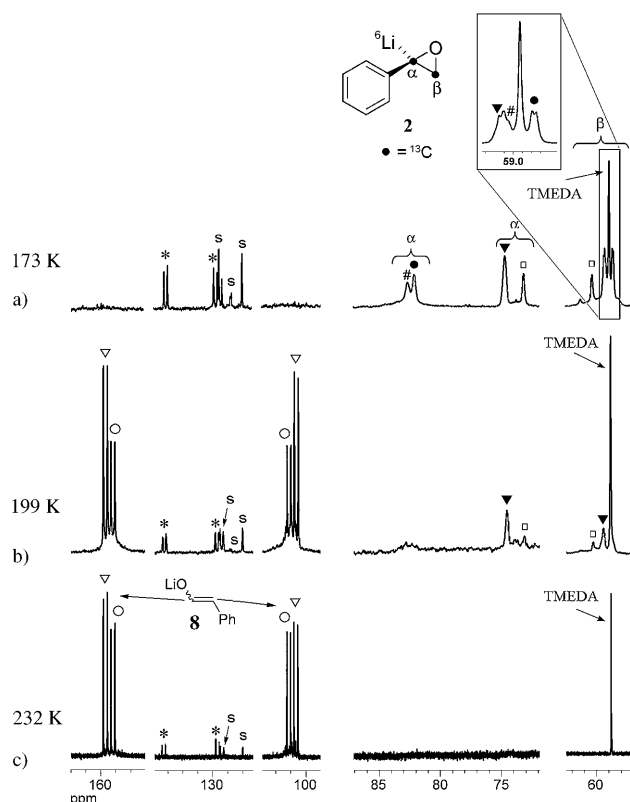
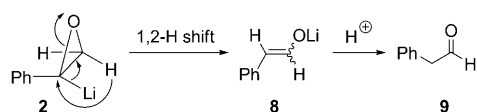


Figure 13. ^{13}C NMR spectra of 0.2 M lithiated $[\alpha, \beta\text{-}^{13}\text{C}_2]\text{styrene oxide}$ obtained using 1 equivalent of $s\text{Bu}^6\text{Li}$ and 3 equivalents of TMEDA at 173 K (trace a), 199 K (trace b), and 232 K (trace c). s stands for starting styrene oxide. Legend: ■ monomer; # stereoisomeric dimers; □ bridged dimer; ▼ tetramer; ▽, ○, * CH vinylic carbon atoms.

crude mixture was phenylacetaldehyde (**9**; Scheme 6). On the basis of these results and considering the large upfield shift associated to two pairs of signals ($\delta=101.3$ and 102.3 ppm), we assigned the above peaks to the vinylic



Scheme 6. 1,2-H Shift rearrangement of α -lithiated styrene oxide **2** leads to phenylacetaldehyde **9** through enolates **8**.

carbon atoms of lithium enolates of phenylacetaldehyde **8** being detected as a mixture of two diastereoisomers (Figure 13c). In fact, such a large high-field shift detected for an sp^2 carbon atom could be explained just in terms of an increase in the π -electron density, as in the case of a “carbonyl carbon atom” of a metal enolate. In the case of the lithium enolate of acetophenone, the two vinylic carbon atoms have been reported to fall in THF at $\delta=97.1$ and 162.5 ppm.^[67] It is reasonable that such a mixture of diastereomeric enolates may stem from a rearrangement of the oxiranylithium through a 1,2-H shift (Scheme 6).^[1f]

Therefore, this type of rearrangement seems to be the preferred ring-opening pathway of α -lithiated styrene oxide after warming the reaction mixture in the absence of organolithium. What also emerges from an analysis of events depicted in Figure 13 is that aggregates with signals between 80.0 – 84.0 ppm (monomer and stereoisomeric dimers) are the most prone to undergo a ring-opening process, followed by that with a signal at $\delta=73.0$ ppm (bridged dimer), whereas the aggregate with a signal observed at $\delta=74.7$ ppm (tetramer) resulted to be the least “reactive”, as one would be expected.^[52] This type of investigation also allowed us to match the carbanionic carbon atoms with signals at $\delta=73.0$, 74.7 and 82.5 ppm to the CH_2 carbon atoms with signals at $\delta=60.3$, 59.2 and 59.1 ppm, respectively.

β -Lithiated styrene oxide: By rigorous inspection, the ^{13}C NMR spectrum obtained from deprotonating $[\alpha,\beta-^{13}C_2]$ styrene oxide with one equivalent of sBu^6Li in the presence of three equivalents of TMEDA at 173 K (0.2 M, Figure 13a) revealed the presence of two more pairs of doublets (because of $^{13}C,^{13}C$ couplings, $^1J(^{13}C,^{13}C)=15$ Hz) at $\delta=61.0$, 61.3 , 61.9 and 62.2 ppm; the pair shifted to high-field being almost three times more intense with respect to the others, all corresponding to C–H carbon atoms (DEPT-135-analysis; Figure 14). They were tentatively assigned to the two C–H

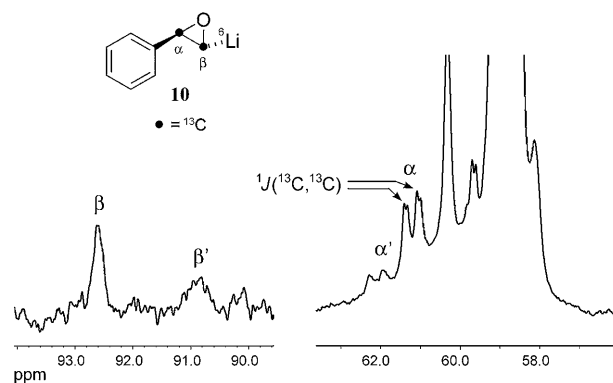
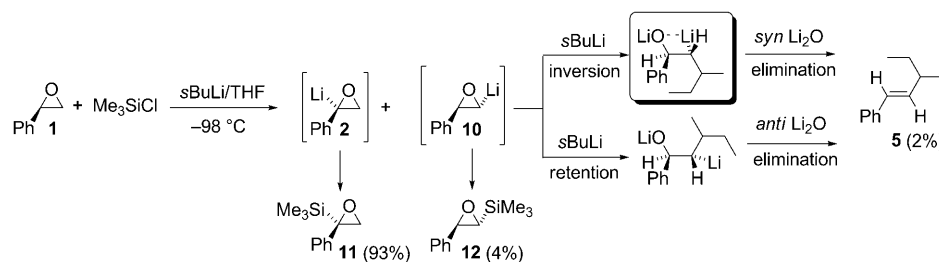


Figure 14. Partial ^{13}C NMR spectrum of 0.2 M lithiated $[\alpha,\beta-^{13}C_2]$ styrene oxide in $[D_8]THF$ at 173 K obtained using 1 equivalent of sBu^6Li and 3 equivalents of TMEDA. Regions displayed show, in particular, signals relating to α -(α' -) and β -(β' -) carbon atoms representative of different aggregates of β -lithiated $[\alpha,\beta-^{13}C_2]$ styrene oxide.

carbon atoms with signals at $\delta=90.8$ and 92.6 ppm (which appeared as broad poorly resolved signals, again in a relative ratio of ca. 3:1) because, as the temperature is increased, the intensities of all the aforementioned peaks tended simultaneously to go down until disappearing. One possible interpretation of the above results is that styrene oxide might also undergo a β -lithiation to some extent (less than 5%) to give **10** (Figure 14). If this is true, this “unstabilised” oxiranylithium should have a stronger carbenoid character than **2** considering the highest δ values exhibited by the carbanionic carbon atoms (β and β' , Figure 14), representative of aggregation states still undefined.

The presence of such a lithiated isomer would also provide a rationale to the formation in the reaction mixture of *trans*-3-methyl-1-phenyl-pent-1-ene (**5**; Figure 7, Scheme 7) as a consequence of a competitive attack of $sBuLi$ just on



Scheme 7. Competition between α - and β -lithiation of styrene oxide leads to compounds **11** and **12** by means of an in situ quenching with Me_3SiCl . The interference of an intermolecular C–Li insertion reaction leads to alkene **5** through a stereospecific Li_2O elimination.

the β -lithiated position of styrene oxide. This result also implies that the initially formed β -lithiooxirane **10** retains its configurational integrity on the timescale of the reaction and that the final elimination step of Li_2O is stereospecific. Indeed, it has been reported^[1h,68] that in the case of terminal alkyl-substituted epoxides, the metalation occurs at the pri-

Table 1. Comparison of the theoretical and experimental ^{13}C NMR shieldings [ppm]^[a] in free (**2a**) and solvated lithium salt.

Position	Exptl ^[b]	B3LYP/6-311+G(d,p)// B3LYP/6-311+G(d,p)	B3LYP/6-311+G(d,p)// B3LYP/6-31+G(d)		B3LYP/6-311+G(2d,p)// B3LYP/6-31+G(d)		B3LYP/6-311+G(2d,p)// B3LYP/6-31+G(d)	
		2a	2a	[2a (thf) ₂]	[2a (thf) ₃]	2a	[2a (thf) ₂]	[2a (thf) ₃]
α	81.2	109.3	108.9	97.7	80.7	108.6	97.0	80.3
β	58.6	72.2	72.2	68.0	59.3	71.7	67.8	58.9
<i>ipso</i>	162.5	162.8	162.6	168.4	173.7	162.1	167.3	173.0
<i>ortho</i>	122.2	126.0	127.0	127.7	127.3	126.2	126.9	126.4
<i>meta</i>	127.5	133.2	134.1	133.6	133.8	133.2	132.6	132.7
<i>para</i>	119.7	127.8	128.1	125.6	122.9	127.2	124.5	121.8
MUE ^[c]		9.93	10.20	8.17	4.50	9.68	7.40	3.87
SDU ^[d]		9.95	9.65	4.16	4.02	9.64	4.47	3.76
MUE(C _{α} +C _{β})		20.85	20.65	12.95	0.60	20.25	12.50	0.60

[a] Relative to TMS. [b] These values refer to the [D₈]THF-solvated monomeric species, in absence of TMEDA, at 173 K. [c] Mean unsigned (absolute) error. [d] Standard deviation on unsigned values.

mary carbon atom, generally from the less hindered site with a high *E* selectivity particularly when using secondary and tertiary alkyl lithium species.

To support the hypothesis that a stereospecific *anti*- β -deprotonation really competes with α -deprotonation, a solution of styrene oxide in THF (0.5 M) containing 1.2 equivalents of (CH₃)₃SiCl was treated with 1.2 equivalents of *s*BuLi at 173 K (in situ quenching conditions). Besides the expected α -trimethylsilylstyrene oxide (**11**) from **2** (93%), 5% of *trans*- β -trimethylsilylstyrene oxide (**12**)^[69] from **10** was also isolated together with 2% of alkene **5** (Scheme 7). Provided that an *anti*-metalation reaction occurs, the stereospecific formation of the *trans*-alkene **5** may be consistent either with an *anti*-substitution reaction followed by a *syn*-Li₂O elimination or with a *syn*-substitution reaction followed by an *anti*-Li₂O elimination (Scheme 7). As the coordination between lithium and oxygen is highly favourable because of the high lattice enthalpy of Li₂O (2799 kJ mol⁻¹),^[70] a *syn*-elimination of Li₂O seems to be the most likely to occur.

Gauge independent atomic orbital (GIAO) calculations:

The intriguing downfield ^{13}C shifts observed for the carbanionic carbon atoms of the monomer and the mixture of stereoisomeric dimers with partially C _{α} -Li broken bonds, as well as the upfield ^{13}C shift presumably related to a four-centre dimer, raise the question whether they accord or not with a theoretical model. To check this, NMR shielding tensors were predicted with the gauge independent atomic orbital (GIAO) method^[71] (see Computational Methods). Structures and NMR shielding values for neutral and both the free and solvated lithium salt of styrene oxide were calculated

and results are summarised in Table S5 in the Supporting Information and in Table 1. As it can be noted, chemical shifts were nicely reproduced by the calculations for the β - and the α -carbon atom of monomeric oxiranyl lithium only when a third molecule of THF is introduced (MUE(C _{α} +C _{β}) 0.60 ppm) (Table 1). An even larger downfield shift was predicted for the α -lithiated carbon atom in the case of free nonsolvated species, which, therefore, should have a stronger carbenoid character. But, what about the dimers? Again, a good agreement between the experimentally observed values (MUE 1.40 ppm) and the calculated chemical shieldings could be found for the main homochiral diastereomeric aggregate, namely [**4c**(thf)₂], shifted downfield with respect to the monomer (entry 3, Table 2).^[72] The calculations predict a more downfield shift and thus more carbenoid character at the α -carbon for all the solvated dimers ([**4a**(thf)₂]-[**4d**(thf)₂]; Table S6, Supporting Information). The observation of a more upfield shift for the C _{α} atom upon solvation as found for the monomer was reproduced for the homochiral dimers ([**4b**(thf)₂] and [**4c**(thf)₂]). However, a more downfield shift was observed for the heterochiral isomers [**4a**(thf)₂] and [**4d**(thf)₂] (Table S6, Supporting

Table 2. Comparison of experimental and theoretical C _{α} and C _{β} ^{13}C NMR shieldings [ppm]^[a] in solvated dimers (**4**) of lithiated styrene oxide.

	Position	Exptl	[4a (thf) ₂]	[4b (thf) ₂]	[4c (thf) ₂]	[4d (thf) ₂]	[4e (thf) ₂]
1	α	82.35 ^[b]	94.0	87.9	86.5	93.8	69.4
	β	58.85 ^[b]	61.4	65.5	62.1	61.7	55.4
	MUE		7.10	6.10	3.70	7.15	8.20
2	α	81.8 ^c	94.0	87.9	86.5	93.8	69.4
	β	58.85 ^[c]	61.4	65.5	62.1	61.7	55.4
	MUE		7.38	6.38	3.98	7.43	7.93
3	α	83.8	94.0	87.9	86.5	93.8	69.4
	β	62.0	61.4	65.5	62.1	61.7	55.4
	MUE		5.40	3.80	1.40	5.15	10.50
4	α	73.0	94.0	87.9	86.5	93.8	69.4
	β	60.3	61.4	65.5	62.1	61.7	55.4
	MUE		11.05	10.05	7.65	11.10	4.25
5	α	83.2	94.0	87.9	86.5	93.8	69.4
	β	58.1	61.4	65.5	62.1	61.7	55.4
	MUE		7.05	6.05	3.65	7.10	8.25

[a] Calculated using B3LYP/6-311+G(d,p)//B3LYP/6-31+G(d), and relative to TMS. [b] The mean value of the shifts for the downfield shifted diastereomer of [**4b**(thf)₂]. [c] The mean value of the shifts for the upfield shifted diastereomer [**4b**(thf)₂].

Information). For the β -carbon, the signals for both the monomer and the dimers experience a more upfield shift upon solvation (Table 1 and Table S6, Supporting Information). Interestingly, none of the dimers ($[4a(thf)_2]$ – $[4d(thf)_2]$) fitted with the upfield shift of the signal at 73.0 ppm found for C_α in one of the co-existing aggregates. Therefore, a solution to this was sought by introducing additional structures (Figure S14, Supporting Information). The only structure that fitted with such an upfield shift (MUE 4.25 ppm) was found when lithium was constrained to coordinate only to the C_α atoms ($[4e(thf)_2]$), thus without oxirane oxygen coordination (Scheme 4 and entry 4, Table 2). We therefore assign the signals at 73.0 and 60.3 ppm to the C_α and C_β atoms, respectively, of such a structure, possibly with additional solvent molecules coordinated. The assignment of the broad peak at 83.2 ppm originating from heterochiral isomers was found less accurate (entry 5, Table 2), and might therefore involve complexes with different solvent shell than modelled. A slight shift was also observed for the four peaks between 81.2–82.5 ppm assigned to the two equilibrating diastereoisomers of $[4b(thf)_2]$ (entries 1 and 2, Table 2); this might be due to the dynamic effect experienced by these isomers.

Natural bond orbital (NBO) analysis: In addition to the NMR analysis on the carbenoid character exhibited by both monomer **2a** and dimers **4** and their solvated analogues presented above, we have analysed the energies of the σ and σ^* orbitals in the oxirane ring. As described in previous studies by Boche and co-workers in the case of carbenoid species,^[7] a lowering of the energy of the $\sigma^*_{O-C_\alpha}$ orbital and simultaneously an elevation of the energy of the σ_{O-C_α} orbital is expected for styrene oxide when it is lithiated, resulting in a decreased energy gap (ΔE) between the two orbitals. A comparison of the orbital energies calculated using NBO analysis, as seen in Table S7 (Supporting Information), shows that on going from the neutral styrene oxide to the lithiated unsolvated monomer **2a**, ΔE is lowered from 0.93 to 0.66 au. The largest contribution to this is the elevation of the σ_{O-C_α} orbital, while the lowering of the $\sigma^*_{O-C_\alpha}$ orbital contributes less. Tri-solvation of monomer **2a** enlarges ΔE mainly because of elevation of the $\sigma^*_{O-C_\alpha}$ orbital, which in fact now has an energy that is higher than the corresponding orbital energy in the neutral compound. At a first glance, looking at only the energy of the $\sigma^*_{O-C_\alpha}$ orbital, one could interpret the data as the lithiated compound $[2a(thf)_3]$ having less carbenoid character than the neutral compound. However, since we know from both the NMR experiments and GIAO calculations that the chemical shift for the α -carbon is shifted downfield upon lithiation, the interpretation needs to be based on the ΔE value.

Dimerisation of **2a** leading to a dimer such as **4c** results in a ΔE of 0.71, thus in between **2a** and $[2a(thf)_3]$ of which, again, the major contribution to the energy change is from the elevation of the σ_{O-C_α} orbital. Subsequent solvation gives $[4c(thf)_2]$, which has a computed ΔE of 0.73. Here, the solvation has a smaller effect on the $\sigma^*_{O-C_\alpha}$ orbital than that

observed for the monomer and the value indicates that $[4c(thf)_2]$ has a stronger carbenoid character than its solvated counterpart $[2a(thf)_3]$. In conclusion, the analysis of the NBO energies is in line with NMR analysis, which indicates that a O-coordinated, bridged dimer such as $[4c(thf)_2]$ has a stronger carbenoid character than $[2a(thf)_3]$ and also in line with available experimental data.

Factors affecting the carbanionic/carbenoid reactivity of lithiated styrene oxide: Factors responsible of a nucleophilic/electrophilic behaviour of lithiated styrene oxide at 173 K in a polar solvent such as THF (which are our standard conditions) were also experimentally investigated. We set up the following experiments on the laboratory scale: two solutions of styrene oxide **1** in THF with different concentrations (0.05 and 0.5 M) were treated separately, at 173 K, each one with 1.2 equivalents of *s*BuLi preliminarily in absence of TMEDA and the resulting mixtures quenched one hour after with CH_3OD . In both cases, the amount of alkene **5**, formed from a “reductive alkylation” process, was very low (3–5 %), with the percentage of α -deuteration of $[D_1]$ -**1** ranging from 82 to 93 (0.05 and 0.5 M, respectively; Table 3).

Table 3. Competitive formation of byproducts **5** and **13** in deprotonation/deuteration of styrene oxide **1** in THF at 173 K according to the presence or absence of TMEDA and to the molar concentration.

molar concentration	TMEDA equiv	epoxide $[D_1]$ 1 [% D] ^[a,b]	alkene 5 [%] ^[b]	diol 13 [%] ^[b]
0.05	–	82	3	< 1
0.5	–	93	5	15
0.05	1	84	4	2
0.5	1	73	2	4
0.05	3	96	3	2
0.5	3	95	2	4

[a] Deuterium incorporation was established by 1H NMR analysis.
 [b] Relative ratios were established by 1H NMR analysis on the crude reaction mixture.

However, in the case of 0.5 M solution, in addition to the above byproduct, a mixture of diastereomeric enediols **13** (d.r. ca. 2:1; as the result of an “eliminative dimerisation” reaction between two units of lithiated styrene oxide) was also isolated in 15 % yield, whereas employing a 0.05 M solution the formation of enediols **13** dropped back to less than 1 % (Table 3). By adding TMEDA to a 0.05 M solution of styrene oxide **1** in THF, the only difference detected was just the increase in the percentage of α -deuteration of $[D_1]$ -**1** from 84 (1 equiv TMEDA) to 96 % (3 equiv of TMEDA), the percentage of alkene **5** and enediols **13** being always rather low, 3–4 (1–3 equiv TMEDA) and 2 % (1–3 equiv TMEDA), respectively. On the other hand, in the case of

0.5 M solution, the percentage of deuteration increased from 73 (1 equiv TMEDA) up to 95 % (3 equiv TMEDA), whereas that of alkene **5** and enediols **13** remained around 2 (1–3 equiv TMEDA) and 4 % (1–3 equiv TMEDA), respectively. In summary, dilution, favouring the monomeric species, which has a lower carbenoid character with respect to stereoisomeric dimers (**4a–4d**), is surely a crucial factor in favouring a nucleophilic/basic behaviour for lithiated styrene oxide at a temperature as low as 173 K also in absence of TMEDA. At a higher concentration, lithiated styrene oxide is more prone to self-associate to give higher aggregates such as dimers **4a–4d** with partially C_α –Li broken bonds, which proved to have a more pronounced “carbene-like” reactivity and are most probably responsible of the formation of the diastereomeric enediols **13**; this is because the higher the concentration of solution, the higher the amount of these type of dimers formed. This tendency may be cut down by adding TMEDA to the reaction mixture.

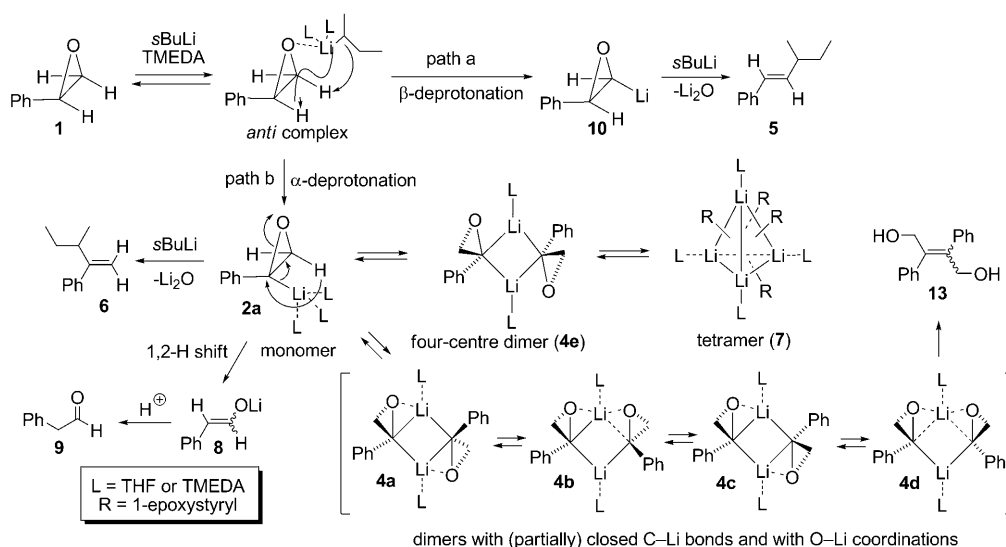
Another factor able to tune the type of reactivity of lithiated styrene oxide is the temperature: at a temperature higher than 173 K, α -lithiated styrene oxide tends to be easily attacked by excess *s*BuLi (if any) to give alkene **6** (“reductive elimination” reaction, see Figure 7) as well as to undergo 1,2-H shift to give phenylacetaldehyde **9** (Scheme 6). Moreover, because β -deprotonation competes to some extent, the presence of alkene **5** in the reaction mixture cannot be avoided also at 173 K (Scheme 8).

Conclusions

In conclusion, the dichotomic reactivity exhibited by lithiated styrene oxide in THF has been related to the aggregation states favoured in solution according to the employed experimental conditions: diluted or concentrated solutions, higher

or lower temperature than 173 K, presence or absence of TMEDA. DFT calculations by using B3LYP suggested that in THF, lithiated styrene oxide may be present as a di-solvated bridged dimer or as a tri-solvated monomer. The latter, with no coordination between Li and the oxirane ring oxygen and with an almost tetrahedral arrangement around the carbanionic carbon, is the most stable species with a negligible delocalisation of the π charge into the phenyl ring (not higher than 10 %).

A multinuclear magnetic resonance investigation performed on lithiated [α,β - $^{13}C_2$]styrene oxide (obtained deprotonating the parent epoxide with both *s*Bu⁷Li and *s*Bu⁶Li) showed that α -lithiated styrene oxide (in agreement with calculations) is mainly present in THF at 173 K, over a range of concentration 0.075–0.3 M, as a THF-solvated monomeric species (**2a**) in equilibrium with dimers (**4**), the NMR signals of which are shifted more downfield (Scheme 8). However, NMR spectra resulted to be actually more complicated than expected, because of the possibility of multiple stereoisomers in solution, in particular for the dimeric aggregates **4**. A factor of further complication was also the reduced symmetry of some aggregates mainly because of the partial breaking of some C_α –Li bonds. These findings were supported by GIAO chemical shift calculations, which are in good agreement with the experimental values found for both the solvated monomer **2a** and the dimers **4**. NMR studies performed on the optically active lithiated (*S*)-[α,β - $^{13}C_2$]styrene oxide, together with concentration-dependent studies, indicated that at least two homochiral dimers (such as [**4b**(thf)₂] and [**4c**(thf)₂]) should be involved. One of these ([**4b**(thf)₂]) is mainly present as a mixture of two diastereomers in slow equilibration on the NMR timescale, each having a pair of diastereotopic lithiated carbon atoms because of the chirality at lithium (Scheme 5). Increasing amount of TMEDA seems to promote a faster



Scheme 8. Proposed two-step mechanism for α - and β -lithiation of styrene oxide and for the formation of alkenes **5** and **6**, enediols **13** and $PhCH_2CHO$ **9** through different aggregation states.

exchange on the NMR timescale between the above epimers at lithium. In addition to the aforementioned aggregates, signals corresponding to two other types of aggregates slowly equilibrating on the NMR timescale could be seen at a higher field. A $^{13}\text{C},^7\text{Li}$ HMQC shift correlation, in addition to confirm the presence of the monomer **2a** (doublet, $^1J(^{13}\text{C},\text{Li})=34\text{ Hz}$), suggested that the highest field shifted aggregates may be assigned to a homochiral four-centre carbon-only chelated dimer (such as **4e**; triplet, $^1J(^{13}\text{C},\text{Li})=16\text{ Hz}$) and a fluxional tetrameric aggregate (**7**), the cross-peak of which was the only one seen in the 2D experiment once it was set up with an optimised $^1J(^{13}\text{C},\text{Li})=10\text{ Hz}$ (Schemes 4 and 8). The intriguing high-field shift observed for the signals of the bridged dimer **4e** with respect to the mixture of O-coordinated stereoisomeric dimers (**4a**(**4d**), **4b**, **4c**, low-field shifted) was also supported by GIAO calculations.^[73]

The above 2D-HMQC experiment, which is described for the first time in the present paper, is undoubtedly a new and invaluable tool for structural studies of organolithium compounds in solution and which complements other routine NMR techniques. Dilution was also proven to be a crucial factor in favouring the monomeric aggregate in solution versus dimeric aggregates with signals that are shifted to low-field, the latter being also the expression of a higher “carbene-like” reactivity of lithiated styrene oxide. In support of this, NBO analysis indicated that a O-coordinated bridged dimer such as [**4c**(thf)₂] should have a higher carbenoid character than monomer [**2a**(thf)₃]. Most probably, such dimeric aggregates might also be directly responsible of the formation of enediols **13** (which are eliminative dimerisation products) as their relative amounts increase at a higher solution concentration in parallel with the increase of dimers concentration (Scheme 8). In order to rationalise all the experimental results described in the present paper, a reasonable hypothesis is that lithiation of styrene oxide could be described, on the whole, as a two-step process in which the formation of a reactive pre-lithiation *anti* complex (with respect to the phenyl group) between the substrate and a monomeric *s*BuLi anticipates a rate-determining proton transfer (Scheme 8). Such complexes have also been previously postulated by Crandall^[5a] and Molander^[74] for rationalizing the regio- and stereoselectivity of numerous α - and β -deprotonation reactions. Starting from the above chelated structures, two competitive pathways may operate for the lithiation of styrene oxide to occur: α - (path b) and β -deprotonation (path a). Once the most acidic α proton has been extracted within the *anti* complex, the corresponding α -lithiated species **2a** may undergo a reductive alkylation reaction and/or a 1,2-H shift reaction to give alkene **6** or phenylacetaldehyde **9** (through enolates **8**), respectively, according to whether the reaction mixture is warmed to room temperature in the presence or absence of *s*BuLi (Scheme 8). At the same time, β -lithiation competes to some extent (5%). The highest downfield shifts observed for the signals corresponding to aggregation states (not further investigated) of β -lithiated styrene oxide **10** at 173 K in

the presence of three equivalents of TMEDA would testify its stronger electrophilic character with respect to **2a**. Indeed, once styrene oxide is lithiated with *s*BuLi, the formation of *trans*-alkene **5**, as a consequence of a reductive alkylation reaction promoted by the organolithium on the β -lithiated regioisomer, cannot be avoided in any way.

In conclusion, lithiated styrene oxide would represent another wonderful example on the “theme of polarities”^[75] as its carbanionic/carbenoid character would be just the poles of another duality. The best explanation to justify the efforts made by the authors of the present paper to unravel the “secrets” and decode the “language” of such a double-faced lithiated system may be found in the words of Roald Hoffmann: “Tension gives life, the potential of change... Each fact or process of the science, and the way these are viewed, is in precarious balance between polar extremes. And the polarities of substances and their transformations resonate with forces deep in our psyche”.^[75] Styrene oxide “progeny”, we are sure, will have in store new interesting and exciting surprises.

Experimental Section

General: Glassware was dried overnight in a 120°C oven (syringes and Teflon-containing parts were dried at 50°C in a vacuum oven) before being transferred into a glovebox (Mecaplex GB 80 equipped with a gas-purification system that removes oxygen and moisture) under a nitrogen atmosphere. The typical moisture content was less than 0.5 ppm. All handling of the lithium compounds was carried out in the glovebox with gas-tight syringes. 2-Chlorobutane, cyclohexane and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) were distilled under a nitrogen atmosphere over CaH_2 . Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under N_2 . [D_8]THF was stored over molecular sieves (4 Å) in the glovebox. Styrene oxide was of commercial grade (97%, Sigma–Aldrich). Commercial solution of *s*BuLi (1.3 M in cyclohexane) was handled with septum and syringe-based technique and titrated against dry THF using *N*-pivaloyl-*o*-toluidine prior to use.^[76]

Preparation of *s*Bu⁶Li: A block of ^6Li metal (0.25 g, 41.6 mmol, 96% ^6Li purchased from Aldrich) was cut into small pieces using a sharp knife. The ^6Li metal was transferred into a 50 mL two-neck flask equipped with silicone/Teflon septa. After this, dry cyclohexane (10 mL) was added and the flask was put in an ultrasonic bath at 20°C (Sonorex Super 10P operated at maximum effect) for about 3 min. Then, the mixture of lithium hydroxide and cyclohexane was removed with a syringe, under a positive pressure of argon, and another aliquot of cyclohexane (10 mL) was added followed by ultrasonic bath for another 3 min. This procedure was repeated several times until the cyclohexane solution remained clear and the previously black lithium pieces had metallic surfaces. Upon addition of dry cyclohexane (15 mL), followed by slow addition of 2-chlorobutane (2.09 mL, 20.0 mmol) over 5 min, the flask was again put in the ultrasonic bath for another 3 h at about 7°C. The reaction started immediately and was monitored by the change of the colourless solution to deep purple. After 12 h of magnetic stirring at 10–15°C under argon, the resulting purple suspension was centrifuged and the supernatant was transferred into a glass apparatus equipped with high-vacuum Teflon valves. The solvent was removed under vacuum (10^{-4} torr). The concentration was about 10 M determined by a titration by NMR spectroscopy by using diisopropylamine (with less than 5% alkoxides). The *s*Bu⁶Li was stored under argon atmosphere in a glass apparatus at –30°C.

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 , ^{13}C triple-resonance probe-head including a z-gradient coil at the following frequencies: 599.944 (^1H), 150.856 (^{13}C), and 233.161 MHz (^7Li). ^{13}C NMR spectra were referenced internally to the C–O carbon atom of $[\text{D}_8]\text{THF}$ ($\delta=67.45$). Exponential multiplication (LB) of 2–6 Hz was applied to ^{13}C spectra. ^7Li spectra were referenced externally to 0.3 M LiCl in $[\text{D}_4]\text{MeOH}$ ($\delta=0.0$). The typical pulse widths for 90° pulses (μs) and attenuation levels (dB, in brackets) were the following: ^{13}C : 12.50 (3.50); ^7Li : 15 (1.50); ^7Li -dec: 100 (18). The probe temperature was calibrated using a methanol thermometer. 2D ^{13}C , ^{13}C -COSY was performed as reported.^[77] The multiplicities are denoted as follows: s=singlet, d=doublet, m=multiplet, dm=doublet of multiplets. Selected ^7Li , $^{13}\text{C}\{^1\text{H}\}$ HMQC parameters: sweep width F_1 (^{13}C) 240 ppm, F_2 (^7Li) 10 ppm; 4 scans per increment in F_2 ; 256 increments recorded; final matrix after zero filling, $1024 (F_2) \times 1024 (F_1)$; evolution delay, Δ_2 , of $^1\text{J} (^{13}\text{C}, ^7\text{Li})$ variable from 8.3 to 50 ms, as described in the main body of this paper; relaxation delay 1 s; acquisition time 0.11 s; sine multiplication of $\pi/2$ in F_2 and Gaussian multiplication of LB=0.30, GB=0.1 in F_1 prior to transformation (magnitude mode); total exp. time 19.22 min.

NMR spectroscopy: representative procedure for the preparation of 0.2 M sample of lithiated styrene oxide at 173 K: An appropriate amount of $s\text{BuLi}$ (77 μL , 0.1 mmol, 1.3 M in cyclohexane), preliminary 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 $[\text{D}_8]\text{THF}$ (0.3 mL) at 173 K (methanol/liquid nitrogen bath). In a separate small flask, a weighted amount (12 mg, 0.1 mmol) of styrene oxide was dissolved in $[\text{D}_8]\text{THF}$ (0.2 mL) and the resulting solution was then slowly added through a gas-tight syringe to the solution of $s\text{BuLi}$. The resulting reaction mixture was then shaken and immediately put in the NMR probe pre-cooled to 173 K. In the case of a titration (or dilution) experiment, for each addition the sample was ejected and placed in a 173 K bath, the Omnifit valve was opened, a desired amount of co-solvent (or solvent) was added, and the desired NMR experiments were run.

Preparation of (α,β - $^{13}\text{C}_2$)-styrene oxide. 3-Chloroperbenzoic acid (459 mg of 75% $m\text{CPBA}$, 2 mmol) was added portionwise over a 15 min period to a cold (ice bath) stirring solution of (α,β - $^{13}\text{C}_2$)styrene (200 mg, 1.89 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was gradually warmed to room temperature and stirred for additional 2 h; then, it was diluted with hexane (30 mL) and the precipitate (3-chlorobenzoic acid) removed by filtration. The filtrate was washed with a 1:1 mixture of 5% aq NaHCO_3 and 5% aq NaHSO_3 (25 mL), then with aq NaOH 1 M (25 mL), and finally with brine and dried over anhyd Na_2SO_4 . The solvent was removed under reduced pressure and the crude product purified by flash column chromatography (silica gel; hexane/ Et_2O 98:2, $R_f=0.3$) to give (α,β - $^{13}\text{C}_2$)styrene oxide (176 mg, 76%). ^1H NMR (600 MHz, $[\text{D}_8]\text{THF}$, 25°C): $\delta=7.26$ – 7.33 (m, 5H; 5ArH), 3.75 (dm, $^1\text{J} (\text{C,H})=175.2$ Hz, 1H; CH), 3.01 (dm, $^1\text{J} (\text{C,H})=175.4$ Hz, 1H; CH_2), 2.65 ppm (dm, $^1\text{J} (\text{C,H})=175.4$ Hz, 1H; CH_2); ^{13}C NMR (150 MHz, $[\text{D}_8]\text{THF}$, 25°C): $\delta=137.9$ (d, $^1\text{J} (\text{C,C})=56.5$ Hz, *ipso*-C), 129.1 (d, $^2\text{J} (\text{C,C})=4.4$ Hz; 2 CH), 128.6 (s, CH), 126.2 (d, $^3\text{J} (\text{C,C})=2.5$ Hz; 2 CH), 52.4 (d, $^1\text{J} (\text{C,C})=27.9$ Hz; CH), 51.2 ppm (d, $^1\text{J} (\text{C,C})=27.9$ Hz; CH); MS (70 eV): m/z (%): 122 (28) [M^+], 121 (33) [M^+-H], 93 (27), 92 (100) [$^{13}\text{CC}_6\text{H}_7^+$] 91 (50), 90 (61). Optically active (*S*)-(α,β - $^{13}\text{C}_2$) styrene oxide was prepared by hydrolytic kinetic resolution, likewise as reported.^[53]

Computational methods: Compounds were optimised at the B3LYP/6-31+G(d) level of theory using Gaussian 98.^[78] Single-point energy calculations were also performed at the B3LYP/6-311+G(d,p)/B3LYP/6-31+G(d) level of theory. All geometries were characterised as minima on the potential-energy surface by using the sign of the eigenvalues of the force-constant matrix from a frequency calculation. NMR chemical shielding tensors were calculated at the B3LYP/6-311+G(d,p)/B3LYP/6-31+G(d) or B3LYP/6-311+G(2d,p)/B3LYP/6-31+G(d) levels of theory by using the GIAO approach as implemented in Gaussian. TMS in T_d symmetry was used as a reference substance for the chemical shielding calculations. The figures of molecular structures were generated by using the Chemcraft program (<http://www.chemcraftprog.com>).

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- [36] Lowering further the temperature of a 0.2 M $[\text{D}_8]\text{THF}$ sample of lithiated styrene oxide, solution viscosity considerably increased just below 170 K, because of the closeness of the freezing point of the solution. It is also worth noting that in the presence of a less polar solvent such as $[\text{D}_{10}]\text{Et}_2\text{O}$ a precipitate formed in the NMR tube even at 173 K most probably because of low reagent solubility. Therefore, all NMR experiments were run at 173 K employing $[\text{D}_8]\text{THF}$ as the solvent system of choice.
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- [55] In principle, with our special triple resonance probehead (with the inner coil selectively tuned to ^{13}C frequency and the outer coil tunable between the frequencies of ^7Li (see the Experimental Section) such a two-dimensional NMR shift correlation, based on scalar spin–spin coupling, may be performed. However, one of the main drawbacks to take into account in setting up this type of experiment is related to the fast relaxation of ^7Li which poses problems for the line-width of the ^7Li resonances; in fact, ^7Li is a nucleus with a moderate quadrupolar moment exhibiting short longitudinal (T_1) and transversal (T_2) relaxation times. As a consequence, the transverse magnetisation arising from broad signals may be completely lost during the preparation delays of the HMQC pulse sequence due to relaxation through T_2 , so that no correlations will be finally observed. This effect will be amplified as the temperature is decreased (see: G. Fraenkel, J. H. Duncan, J. Wang, *J. Am. Chem. Soc.* **1999**, *121*, 432–443). As a precaution to minimise losses of magnetisation along the pulse sequence, the short delay usually inserted between the final ^{13}C pulse and the start of acquisition was eliminated. Because of the higher receptivity of ^7Li with respect to ^{13}C ($R^{\text{Carbon}}(^7\text{Li})/R^{\text{Carbon}}(^{13}\text{C}) = 1590$) we decided to use ^7Li detection; in this way, there would also be the possibility to take advantage of shorter experimental time due to faster relaxation of ^7Li versus ^{13}C . When ^{13}C decoupling is omitted during the acquisition time (t_2), heteronuclear ^7Li , ^{13}C coupling will be effective during FID sampling, thereby leading to cross-peak splitting in F_2 . A low-power ^1H decoupling was also applied during t_2 .
- [56] Total experimental time, t_e , resulted to be 19.22 min. In this case, t_e is mainly determined by the ^7Li relaxation time, the sweep width in F_2 and the number of increments in F_1 . In a similar experiment, but run on a racemic sample of $[\alpha, \beta\text{-}^{13}\text{C}]$ styrene oxide, the number of increments was increased from 256 up to 512 employing also a $\Delta_2 = 4$ ms for a final $t_e = 1.17$ h. However, the new 2D spectrum did not show additional cross-peaks.
- [57] Even if reductive alkylation reactions compete to some extent soon after the lithiation process, most probably with concomitant elimination of Li_2O as byproduct, it seems improbable that a lithium peak may be associated to such a salt because of its complete insolubility in THF. Commercial Li_2O , indeed, proved to be completely insoluble in THF. Moreover, addition of water to a suspension of Li_2O in THF leads to the dissolution of this salt and a peak at $\delta = 0.57$ ppm (referenced externally to 0.3 M LiCl in $[\text{D}_4]\text{MeOH}$) emerges in ^7Li NMR spectrum. This peak most probably refers to LiOH because when a solution was prepared from commercial LiOH in THF/ H_2O , a similar chemical shift value was observed. Therefore, the peak at $\delta = 0.57$ ppm might in principle be assigned to LiOH or to alkoxides, as discussed in the main body of the paper.
- [58] Concentration-dependent studies were frustrated by the very high reactivity of **2**. The only successful and feasible dilutions (in order to obtain “homogeneous” samples to be compared) could only be performed directly in the NMR tube by adding solvent. Any attempt to pull a portion of the sample containing the oxiranyllithium up into a syringe in order to dilute it more, led to a considerable quenching and decomposition of the anion. That is why the “precious” sample of optically active and doubly enriched styrene oxide was only diluted (in the NMR tube) up to a factor of 2. Isolated samples of racemic lithiated styrene oxide, prepared at higher dilution (up to 0.03 M), showed that the various aggregates continued to compete with the monomeric species; however, they were always in slow equilibration on the NMR timescale.
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