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Solvent and TMEDA Effects on the Configurational Stability of Chiral Lithiated Aryloxiranes

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Dedicated to Professor Alfredo Ricci on the occasion of his retirement, who enriched the lives of all he met

Abstract: The employment of hexane/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) dramatically hinders the racemization of those lithiated styrene oxides (trifluoromethyl-, chloro-, and phenylthio-substituted) that have been proven to be configurationally unstable in THF on the timescale of their reactions. The barriers to inversion and the activation parameters, calculated (Eyring equation) for reactions performed in THF, THF/TMEDA, and hexane/TMEDA, suggest the intervention of particular enantiomerization mechanisms for each case. The role of TMEDA in both coordinating and noncoordinating solvents has also been questioned and discussed in light of the kinetic data gathered and a model for deprotonation in hexane/TMEDA has also been proposed. The synthetic benefits of our results became apparent on establishing an asymmetric synthesis of an industrially important antifungal agent.

Keywords: configurational stability · epoxides · kinetics · ligand effects · lithiation · solvent effects

Introduction

Chiral lithium carbenoids are invaluable synthons for the stereoselective synthesis of substituted carbon backbones.[1] However, the question of their configurational stability under the conditions of their generation, thermal lability/stability, dichotomous reactivity (carbanionic/carbene-like behavior),[2] and the steric course of their electrophilic substitutions (retentive and invertive pathways or the intervention of a single-electron-transfer mechanism)[3] are important issues that always need to be addressed before planning an asymmetric synthesis.[4] At the same time, aggregation and solvation are also important factors to be taken into consideration when rationalizing the stereochemical pathway observed[5] because of their influence on the structure–reactivity relationship.[6]

Chiral oxiranyllithiums (which are peculiar Li/OR carbenoids),[1d,2,7] in particular, play increasingly important roles in stereoselective organic synthesis.[8] Although known to be more stable than the corresponding acyclic α-lithiated ethers, the racemization of such key intermediates is always a possibility depending upon the conditions employed.[9]

As part of an ongoing investigation into the structures and dynamics of chiral oxiranyllithiums we recently reported that an *ortho*-positioned *para*-tolylsulfinyl group,[10] as well as *ortho*-, *meta*-, and *para*-positioned trifluoromethyl groups,[11] on the phenyl ring of optically active styrene oxides induce epimerization upon lithiation. Although in practice it is much easier to use reagents that are "configurationally stable", it is intellectually rewarding and fascinating to use "configurationally labile" chiral organolithium species after defining the factors that increase their configurational stability on the reaction timescale. Considerable effort has been and is currently being made to slow down the racemization of stereolabile chiral organolithiums by using different solvents and/or cosolvents that are known to significantly influence the reactivity and configurational stability of organolithiums.[12] However, a general "recipe" for the proper conditions in terms of solvents and ligands able to promote a "fine-tuning" of the racemization rate of a chiral organolithium has not yet been established. This is also because enantiomerization can occur by a number of different and competing mechanisms[13] and the effects of ligands on the inversion barriers are not straightforward. For instance, one of the most useful cosolvents is *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA), which is known to either retard[12c,g,h,13] racemization or accelerate epimerization.[12b,d] We describe herein the effect of TMEDA on the configurational stability of α-lithiated trifluoromethyl-, chloro-, and phenylthio-substituted aryloxiranes in both coordinating and noncoordinating solvents.[14] The role of this ligand will also be tackled in light of the calculated barriers to inversion and activation parameters. A general trend becomes apparent for such reactive intermediates with a

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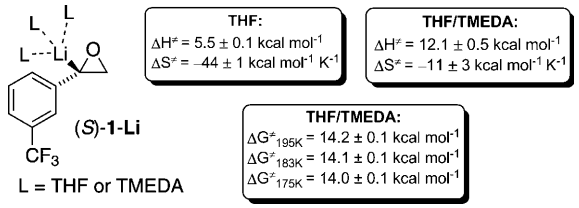
subtle interplay of the different enantiomerization mechanisms involved depending on the stereoelectronic requirements of the aryl substituent.

Results and Discussion

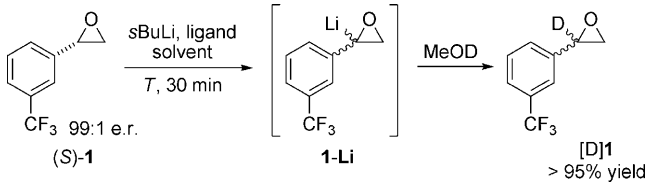
We recently reported[11] the temperature dependence of the racemization rate of (*S*)-**1-Li** (obtained by deprotonating enantiomerically enriched *m*-trifluoromethylstyrene oxide ((*S*)-**1**) with *s*BuLi) in THF ($t_{1/2}=43.4$ min at 175 K, $t_{1/2}=272.4$ min at 157 K).

On the basis of the calculated activation parameters ($\Delta H^{\neq}_{enant}=5.5$ kcal mol^{-1} and $\Delta S^{\neq}_{enant}=-44\pm1$ cal mol^{-1} K^{-1}; Scheme 1), the transformation of a contact ion pair (CIP) into a solvent-separated ion pair (SSIP) was determined to be the rate-determining step. Interestingly, we have now observed that the rate of racemization proved to be dramatically affected by the presence of TMEDA in the reaction mixture and by the nature of the solvent employed. Indeed, when a 0.05 M solution of (*S*)-**1** underwent deprotonation/deuteration with *s*BuLi (1.5 equiv)/TMEDA (1 equiv) in THF, [D]**1** could be recovered after 30 min (175 K) with an enantiomeric ratio (e.r.) of 96:4, 85:15 being the observed e.r. in the absence of the above ligand (entries 1 and 2, Table 1). Surprisingly, upon changing the solvent from THF to hexane (at a reaction temperature of 183 K), the e.r. of [D]**1** mirrored that of the starting epoxide (99:1, entry 3, Table 1).



Scheme 1. Enantiomerization barriers and activation parameters of lithiated *m*-trifluoromethylstyrene oxide ((*S*)-**1-Li**, 99:1 e.r.) in THF in the presence and absence of TMEDA.

Table 1. Lithiation/deuteration of *m*-trifluoromethylstyrene oxide ((*S*)-**1**) at different temperatures and with different solvents.



Entry	Solvent	T [K]	Ligand	D [%][a]	e.r.[b]
1	THF	175	–	>95	85:15
2	THF	175	TMEDA (1 equiv)	>95	96:4
3	hexane	183	TMEDA (1 equiv)	>95	99:1

[a] Evaluated by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined by chiral stationary phase HPLC (see the Experimental Section).

The barrier to enantiomerization of **1-Li** was then calculated for reactions performed in THF in the presence of TMEDA (1 equiv) by determination of the e.r. after quenching with a deuterium source and on aging enantioenriched **1-Li** for different times at 195 K, as previously described.[11] The first-order plot obtained indicated an estimated racemization half-life ($t_{1/2}$) of 10.6 min, which equates to an enantiomerization barrier ($\Delta G^{\neq}_{enant}$) of 14.2 kcal mol^{-1} at 195 K (see the Supporting Information).[15] Similar deprotonation/deuteration kinetic studies were also carried out on **1-Li** after lowering the temperature to 183 and 175 K, at which the free energies of activation for **1-Li** were estimated to be $\Delta G^{\neq}=14.1$ ($t_{1/2}=100.3$ min) and 14.0 kcal mol^{-1} ($t_{1/2}=417.7$ min), respectively (see the Supporting Information).

From these studies, the activation parameters for the enantiomerization of **1-Li** in THF/TMEDA could also be determined. An Eyring plot (Figure 1) revealed an enthalpy of activation ($\Delta H^{\neq}$) of 12.1 ± 0.5 kcal mol^{-1} and an entropy of activation ($\Delta S^{\neq}$) of -11 ± 3 cal mol^{-1} K^{-1}. It has been reported that the relative affinities of TMEDA and THF for lithium are highly substrate-dependent.[16] The above data are consistent with a surprising and successful competition of TMEDA with the bulk THF for coordination sites on lithium. The presence of TMEDA has, in fact, the interesting effect of increasing the enthalpy of activation (C–Li bond breaking), thereby hindering the formation of an SSIP (Scheme 1).

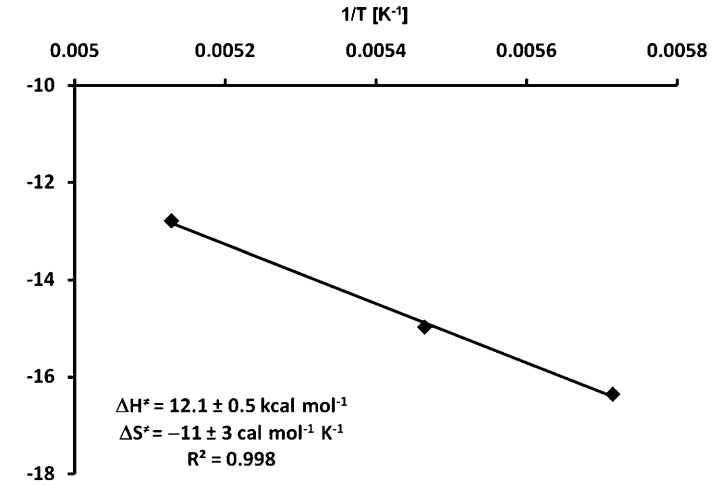


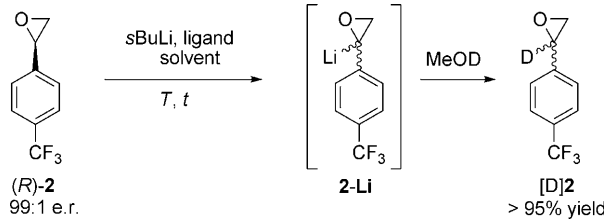
Figure 1. Eyring plot and activation parameters for the enantiomerization of **1-Li**.

This finding is in line with what had previously been found in the case of lithiated styrene oxide[2] for which a multinuclear spectroscopic investigation demonstrated that, at least with reference to the monomeric TMEDA complex, this ligand competed with bulk THF for lithium. Hoffmann and co-workers[12h] pointed out that the fact that some additives (e.g., TMEDA) affect the nature of a CIP does not

necessarily imply that they should facilitate the formation of an SSIP because the direction or magnitude of these effects is not easily predicted in each case. In the case of **1-Li**, in the presence of TMEDA, the nature of the C–Li bond was significantly affected and the racemization rate was reduced considerably in THF and completely blocked in hexane.[17]

α-Lithiated *p*-trifluoromethylstyrene oxide (**2-Li**), generated in THF/Et_2O (3:2) by lithiation of optically active (*R*)-**2** (99:1 e.r.) with *s*BuLi (1.5 equiv), was found to undergo faster racemization than the *meta* isomer **1-Li** even at a temperature as low as 157 K ($t_{1/2}=14$ s, $\Delta G^{\neq}_{enant}=10.1\pm0.1$ kcal mol^{-1}).[11] After a reaction time of 10 s, the corresponding deuterated product [D]**2** was recovered with 61:39 e.r. (entry 1, Table 2). In the presence of TMEDA, a

Table 2. Lithiation/deuteration of *p*-trifluoromethylstyrene oxide ((*R*)-**2**) at different temperatures and with different solvents.

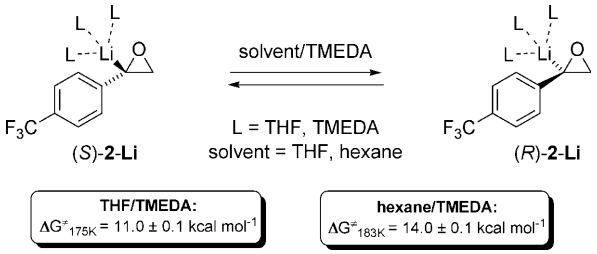


Entry	Solvent	T [K]	t [s]	Ligand	D [%][a]	e.r.[b]
1	THF/Et_2O (3:2)	157	10	–	>95	61:39
2	THF	175	10	TMEDA[c]	>95	60:40
3	THF	175	10	PMDTA[c]	72	56:44[d]
4	hexane	183	15	TMEDA[c]	>95	96:4

[a] Evaluated by ^{1}H NMR analysis of the crude reaction mixture. [b] Determined by chiral stationary phase HPLC (see the Experimental Section). [c] 1 equivalent. [d] Corrected for the percentage deuterium found.

similar e.r. (60:40) was detected for [D]**2**, but this time at a higher temperature, namely 175 K (entry 2, Table 2). By changing the ligand from TMEDA to *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (PMDTA), the addition of MeOD essentially gave racemic [D]**2** (56:44 e.r.) with a lower deuterium content (72% D; entry 3, Table 2). The deprotonation time was maintained at 10 s. Therefore, the employment of this tridentate ligand in THF surprisingly contributed to an increase in the racemization rate. The use of TMEDA in hexane proved to be successful in reducing the racemization of **2-Li**; after a deprotonation time of 15 s, the e.r. of [D]**2** was still as high as 96:4 (entry 4, Table 2).

The activation free energies of enantiomerization ($\Delta G^{\neq}_{enant}$) for **2-Li** in THF/TMEDA and in hexane/TMEDA calculated from the corresponding Eyring equation were 11.0 ± 0.1 kcal mol^{-1} at 175 K ($t_{1/2}$(rac) = 6 s) and 14.0 ± 0.1 kcal mol^{-1} at 183 K ($t_{1/2}$(rac) = 91.1 min), respectively (Scheme 2 and the Supporting Information). Next, the rate of enantiomerization of **2-Li** with varying amounts of TMEDA was investigated in hexane at 183 K. With less than 1 equivalent of TMEDA, the rate of lithiation was reduced significantly (% D ranging from 56 to 87% with 0.3–0.5 equiv TMEDA), and with less than 0.3 equivalents of



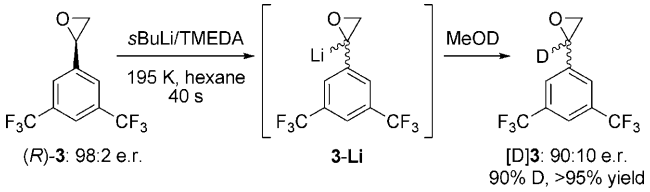
Scheme 2. Enantiomerization barriers of lithiated *p*-trifluoromethylstyrene oxide (**2-Li**) in THF and in hexane in the presence of TMEDA (1 equiv).

TMEDA, anion decomposition was also seriously accelerated (yields below 70%).

On the other hand, in the presence of more than 1 equivalent of TMEDA (3–10 equiv), the enantiomerization rate was similar to that calculated with 1 equivalent of TMEDA. In fact, the corresponding Eyring plots revealed $\Delta G^{\neq}_{enant}$ values for **2-Li** ranging from 14.0 to 14.1 kcal mol^{-1} ($t_{1/2}$(rac) = 91.2–105.0 min) at 183 K.[18] Therefore, for the above-described deprotonation processes, as well as for the other processes (see below), described herein, the employment of just 1 equivalent of TMEDA in hexane proved to be sufficient either to control the configurational stability of the corresponding oxiranyllithiums or to achieve the highest % D and chemical yield for the α-deuterated adducts at a reasonable metalation rate.

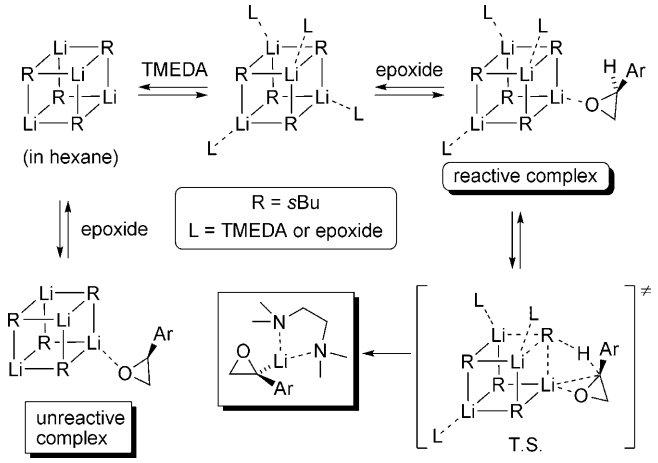
This TMEDA/hexane effect also held for lithiated aryloxiranes with two CF_3 groups in a *meta* orientation. It has been reported[11] that oxiranyllithium **3-Li** (Scheme 3), generated in a polar medium (THF/Et_2O), also undergoes very quick racemization at 157 K to give, after quenching with MeOD, completely racemic [D]**3** after a deprotonation time of 5 s. Interestingly, optically active 3,5-bis(trifluoromethyl)-styrene oxide ((*R*)-**3**; 98:2 e.r.), deprotonated with *s*BuLi/TMEDA (1 equiv) in hexane at 195 K and quenched with MeOD, gave enantioenriched [D]**3** with 90:10 e.r. (90% D, >95% yield) after a deprotonation time of 40 s (Scheme 3).

Now, the following questions need to be addressed. What are the factors responsible for the higher configurational stability of oxiranyllithiums in noncoordinating solvents in the presence of a diamine such as TMEDA? Is this general behavior for styrene oxides with electron-withdrawing substituents? In the first place, it is interesting to observe that in the absence of TMEDA, no deprotonation occurs with *s*BuLi in hexane even when using an excess of this base. Secondly, it is also noteworthy that *s*BuLi exists largely asso-



Scheme 3.

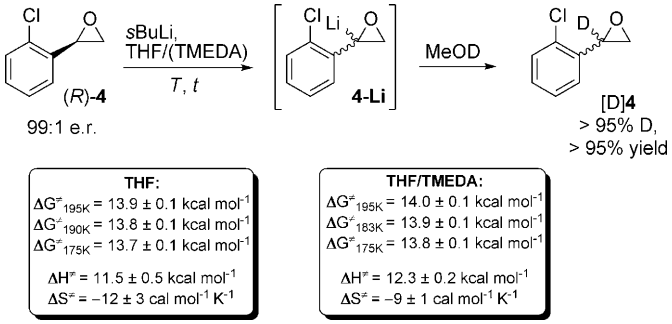
ciated as a tetramer in hydrocarbon solvents (e.g., cyclopentane[19a] and cyclohexane[19b]). Furthermore, kinetic data from Beak and co-workers[19b] suggest that the major interaction of TMEDA with *s*BuLi in cyclohexane is just an addition of such a ligand to aggregated *s*BuLi.[19c,d] Therefore, also in consideration of the fact that the formation of a complex-induced proximity effect (CIPE)[20] is crucial for the lithiation of styrene oxide to take place,[2] we assume, in line with the data reported for the lithiation of carboxamides by Beak and co-workers,[19b] that tetrameric *s*BuLi in hexane binds to oxirane to form a relatively unreactive complex, which is then made more reactive in the presence of TMEDA.[21] Thus, a reactive lithiumorganyl is more likely to be released from its associated lithiums in the transition state (T.S.) of the deprotonation reaction in which TMEDA also provides complexation. Adaptation of Beak's model to the present case leads to Scheme 4.



Scheme 4. Proposed mechanism for the lithiation of styrene oxides in hexane/TMEDA. Lithiated oxirane is shown as a monomeric species for simplicity.

A few years ago, Hoppe and co-workers reported the first highly enantioenriched α-thioallyllithium compound, which showed a remarkable configurational stability in Et_2O and THF but underwent quick racemization in toluene.[22] This behavior was rationalized by Brandt and Haeffner; in the case of coordinating solvents, racemization is hindered by reduced solvent affinity in the transition state, whereas in noncoordinating solvents, the inversion of the configuration is facilitated by aggregation.[5d] In striking contrast to such a α-thioallyllithium compound, as for chiral oxiranyllithiums **1**–**3**-**Li**, inversion takes place almost as quickly in THF, but is considerably slowed down in hexane/TMEDA. It is unlikely that in such a solvent (hexane) the above lithiated oxiranes exist as monomers.[23] In any case, the point is that even though aggregated, they are resistant to fast racemization in hexane/TMEDA.[24]

To establish the scope and limitations of such deprotonation reactions in the presence of TMEDA, the configurational stability of other α-lithiated aryl-substituted styrene oxides was investigated under different conditions of temperature, solvent, and cosolvent. Optically active *o*-chlorostyrene oxide ((*R*)-**4**, 99:1 e.r.; Scheme 5) was deprotonated



Scheme 5. Enantiomerization barriers and activation parameters of lithiated *o*-chlorostyrene oxide (**4**-**Li**) in THF in the presence or absence of TMEDA.

with *s*BuLi in THF for time *t* and quenched with MeOD to give [D]**4** to obtain information about the enantiomerization dynamics of the corresponding lithiated oxirane **4**-**Li**. A plot of $\ln(ee/100)$ versus time (see the Supporting Information) showed good linearity at three different temperatures for reactions performed with or without TMEDA. The corresponding calculated enantiomerization barriers are reported in Scheme 5. The Eyring plots of $\ln(k_{enant}/T)$ versus $1/T$ also show a very good linear relationship over three half-lives for the two sets of reactions and allowed the calculation of the activation parameters: $\Delta H^{\neq} = 11.5 \pm 0.5$ kcal mol^{-1} and $\Delta S^{\neq} = -12 \pm 3$ cal mol^{-1} K^{-1} in THF and $\Delta H^{\neq} = 12.3 \pm 0.2$ kcal mol^{-1} and $\Delta S^{\neq} = -9 \pm 1$ cal mol^{-1} K^{-1} in THF/TMEDA (Figure 2).

If we compare this case with that of lithiated *m*-trifluoromethylstyrene oxide **1**-**Li**, two main differences are worth noting. In the first place, in the case of **4**-**Li**, the enthalpic and entropic barriers to enantiomerization are similar in both the absence and presence of TMEDA, whereas they are quite different for **1**-**Li**. In the second place, both entropies of activation are still negative, but smaller for **4**-**Li** than for **1**-**Li** in the absence of TMEDA.

The results obtained in THF suggest either minimal additional solvation in the transition state or that TMEDA does not affect the C–Li bond strength of **4**-**Li** as strongly as it does for **1**-**Li**. Thus, it is reasonable to think that a different enantiomerization mechanism, such as the "conducted tour" mechanism, may be involved in **4**-**Li** because of favorable intramolecular coordination between lithium and chlorine.[25] Once again, the combined use of a noncoordinating solvent and TMEDA proved to be successful for preserving the configurational stability of **4**-**Li**. In fact, the lithiation of (*R*)-**4** in hexane/TMEDA at 183 K led to (*R*)-[D]**4** with 99:1 e.r. upon quenching with MeOD with a deprotonation time of 12 min (Scheme 6).

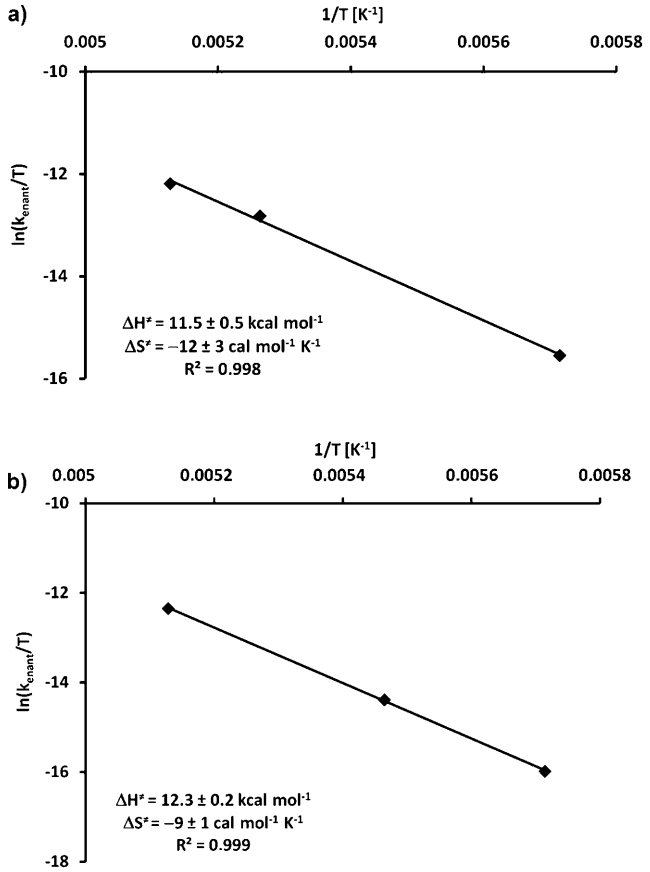
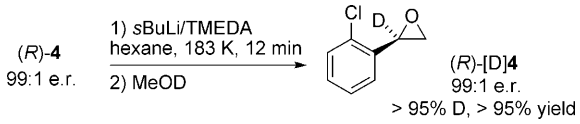


Figure 2. Eyring plots and activation parameters for the enantiomerization of **4**-**Li** in a) THF and b) THF/TMEDA.

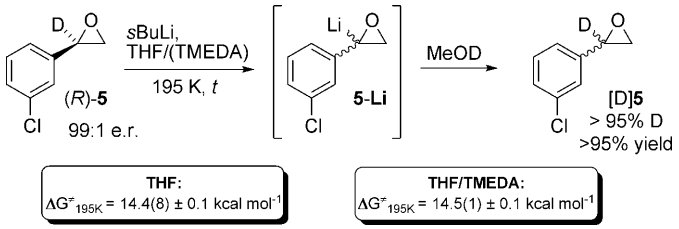


Scheme 6.

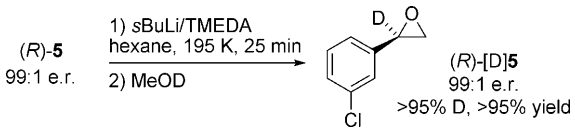
The time-dependent deuteration (see the Supporting Information) of α-lithiated *m*-chlorostyrene oxide (**5**-**Li**) in THF, obtained by deprotonating optically active *m*-chlorostyrene oxide ((*R*)-**5**, 99:1 e.r.) with *s*BuLi (1.5 equiv), revealed enantiomerization kinetics slower than **4**-**Li** with a racemization half-life of 24.3 min at 195 K, which corresponds to an inversion barrier ($\Delta G^{\neq}_{enant}$) of 14.4(8)± 0.1 kcal mol^{-1} (>95% D, >95% yield; Scheme 7).

In the presence of TMEDA (1 equiv), the activation free energy ($\Delta G^{\neq}_{enant}$) calculated for **5**-**Li** almost mirrors the value obtained in THF alone: 14.5(1)±0.1 kcal mol^{-1} ($t_{1/2}$= 26.4 min) at 195 K in THF (>95% D, >95% yield; Scheme 7). Once again, racemization was completely blocked in hexane/TMEDA even at 195 K ((*R*)-[D]**5**: 99:1 e.r., >95% D, >95% yield, reaction time 25 min; Scheme 8).

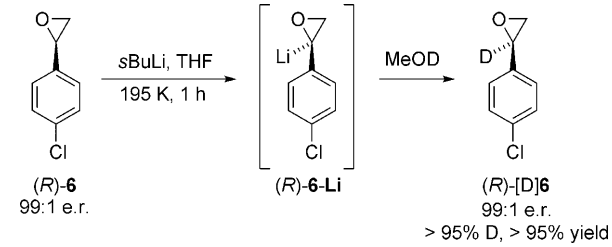
On the other hand, oxiranyllithium **6**-**Li**, generated by treatment of optically active *p*-chlorostyrene oxide ((*R*)-**6**, 99:1 e.r.) with *s*BuLi (1.5 equiv), also proved to be configurationally stable in THF alone at 195 K; quenching the reaction mixture with MeOD gave the deuterated epoxide (*R*)-[D]**6** with the configuration of the benzylic-type carbon atom unaffected (99:1 e.r.), even after 1 h (Scheme 9).



Scheme 7. Enantiomerization barriers of lithiated *m*-chlorostyrene oxide (**5**-**Li**) in THF and THF/TMEDA (1 equiv).



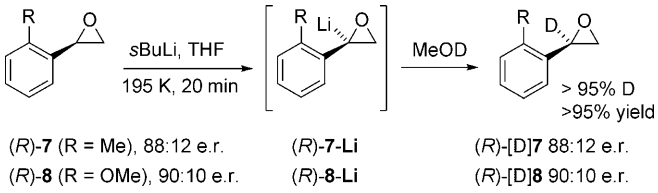
Scheme 8.



Scheme 9.

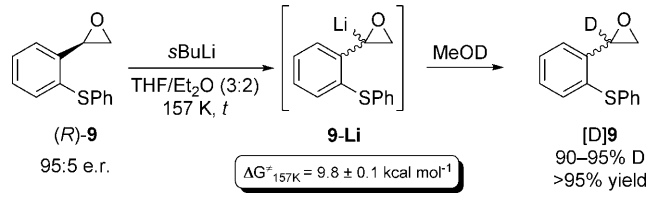
Thus, with regard to the relationship between the electron-withdrawing inductive strength provided by a certain aryl substituent and the configurational stability of the corresponding α-lithiated aryl epoxide, it seems as though a Hammett σ value of 0.37 (with this constant mainly measuring field/inductive effects, as in the case of a *meta*-positioned chlorine atom), is enough to trigger racemization in THF. This is consistent with the fact that lithiated *m*-fluorostyrene oxide (for which σ_m(F)=0.34) is, indeed, configurationally stable.[11,26] Not surprisingly, and in line with what has just been stated, electron-donating groups on the phenyl ring do not affect the configurational stability of lithiated styrene oxides in THF. Both α-lithiated *o*-tolyl- and *o*-methoxyphenyloxiranes (*R*)-**7**-**Li** and (*R*)-**8**-**Li** (generated by treating the optically active epoxides (*R*)-**7** (88:12 e.r.) and (*R*)-**8** (90:10 e.r.) with *s*BuLi (1.5 equiv) in THF) could, indeed, be successfully trapped with a deuterium source to give (*R*)-[D]**7** and (*R*)-[D]**8**, respectively, with the same e.r. as the starting oxiranes (Scheme 10).

Finally, the case of the phenylthio substituent was also investigated. In a preliminary communication we recently re-



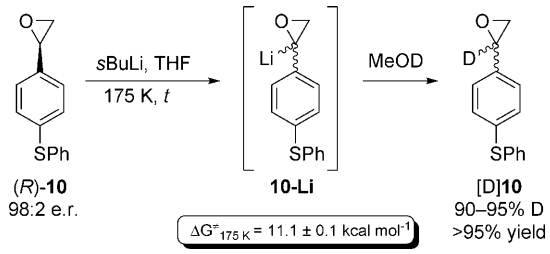
Scheme 10.

ported[27] that although α-lithiated *o*- and *p*-phenylthiostyrene oxides are configurationally unstable at 175 K in THF on the timescale of their reactions, α-lithiated *m*-phenylthiostyrene oxide is not. A series of deprotonation/deuteration experiments have now been performed with optically active *o*-phenylthiostyrene oxide ((*R*)-**9**, 95:5 e.r.; Scheme 11) and *p*-phenylthiostyrene oxide ((*R*)-**10**, 98:2 e.r.;



Scheme 11. Enantiomerization barrier of lithiated *o*-phenylthiostyrene oxide (**9-Li**) in THF/Et_2O.

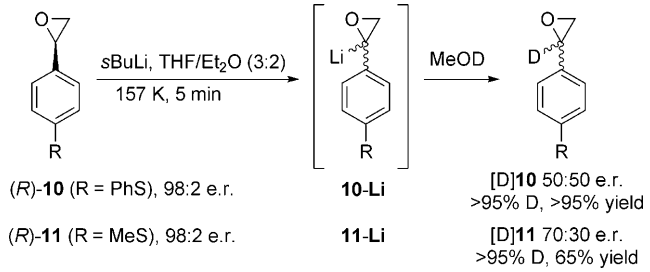
Scheme 12), varying the racemization time from 5 to 30 s, to give deuterated [D]**9** and [D]**10**. From the slopes of the corresponding Eyring plots (see the Supporting Information), the activation free energies ($\Delta G^{\neq}_{enant}$) of the oxiranyllithiums **9-Li** (157 K (THF/Et_2O, 3:2)) and **10-Li** (175 K (THF)) were found to be 9.8 ($t_{1/2}=4$ s) and 11.1 kcal mol^{-1} ($t_{1/2}=8$ s), respectively (Schemes 11 and 12).



Scheme 12. Enantiomerization barrier of lithiated *p*-phenylthiostyrene oxide (**10-Li**) in THF.

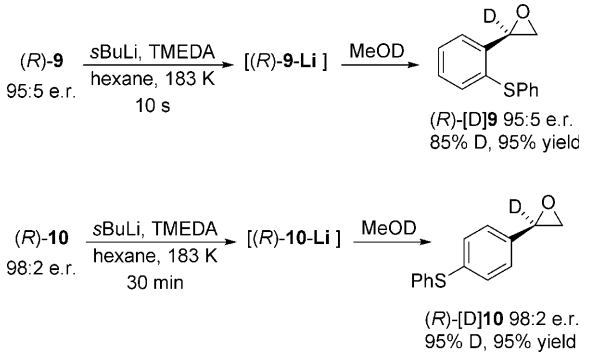
It has been said[27] that when the phenylthio substituent is at the *ortho* or *para* position of the phenyl ring, strong conjugative interactions involving the low-lying 3d orbitals of the sulfur might play a key role in providing stabilization of the above oxiranyllithiums, thereby triggering racemization. To prove this, the outcome of the deprotonation/deuteration of optically active *p*-phenylthiostyrene oxide ((*R*)-**10**) was compared with that of *p*-methylthiostyrene oxide ((*R*)-**11**) in which the CH_3S group has a slightly acidifying effect[28] compared with the PhS group.

After generating oxiranyllithiums **10-Li** and **11-Li** with *s*BuLi (1.5 equiv) at 157 K in THF/Et_2O (3:2), quenching with MeOD gave, after 5 min, deuterated [D]**10** as an essentially racemic mixture and [D]**11**, as expected, with a higher e.r. of 70:30 (Scheme 13).



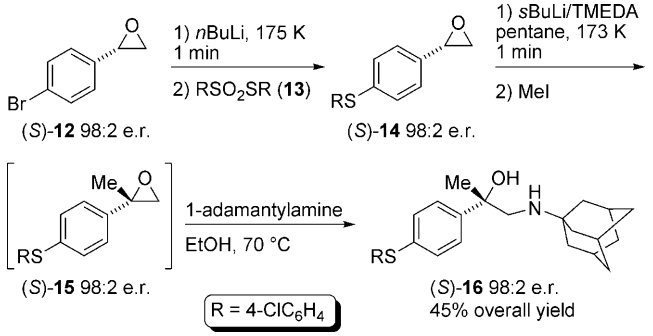
Scheme 13.

Next, the influence of TMEDA on the configurational stability of the above lithiated systems was also evaluated. The reactions of oxiranes (*R*)-**9** (95:5 e.r.) and (*R*)-**10** (98:2 e.r.) in hexane with *s*BuLi (1.5 equiv) in the presence of TMEDA (1 equiv) and the subsequent deuteration with MeOD gave epoxides (*R*)-[D]**9** with 95:5 e.r. (85% D, 95% yield) and (*R*)-[D]**10** with 98:2 e.r. (95% D, 95% yield) after a metalation time of 10 s and 30 min, respectively (Scheme 14). These results are once more consistent with the higher configurational stability that α-lithiated aryloxiranes, such as (*R*)-**9-Li** and (*R*)-**10-Li**, have in hexane/TMEDA.



Scheme 14.

Under the aforementioned conditions, the asymmetric synthesis of a sulfurated amino alcohol such as (*S*)-**16** (Scheme 15), with the properties of an industrially important antifungal agent,[29] was also successfully established. First, optically active *p*-chlorophenylthiostyrene oxide ((*S*)-**14**, 98:2 e.r., 50% yield) was prepared by bromine/lithium exchange in (*S*)-**12** and subsequent coupling with *S*-(4-chlorophenyl) 4-chlorobenzenethiosulfonate (**13**). The deprotonation of (*S*)-**14** with *s*BuLi (1.3 equiv)/TMEDA (1 equiv) in



Scheme 15.

pentane at 173 K (1 min reaction time) followed by quenching with MeI gave the corresponding α-methylated adduct (*S*)-**15** (50% conversion). The latter, without isolation, was then subjected to regioselective ring opening promoted by 1-adamantylamine to furnish the enantiomerically enriched target molecule (*S*)-**16** (98:2 e.r., 45% overall isolated yield; Scheme 15).

Conclusion

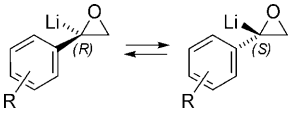
The configurational stability of differently aryl-substituted α-lithiated styrene oxides has been (re)investigated in both coordinating and noncoordinating solvents, and in the presence or absence of TMEDA. Whereas electron-donating groups (e.g., methyl and methoxy) do not alter the configurational stability in THF and at low temperatures, electron-withdrawing groups (e.g., chloro and trifluoromethyl) trigger racemization in THF at a rate dependent on their position on the phenyl ring.

For all those derivatives (**1**–**5**-**Li**, **9**-**Li**, and **10**-**Li**) proven to be configurationally unstable on the timescale of their reactions, the presence of TMEDA in coordinating solvents such as THF often contributes to lowering their rate of enantiomerization (thereby increasing the barriers to inversion $\Delta G^{\neq}_{enant}$), whereas in noncoordinating solvents, such as hexane, all the above oxiranyllithiums showed remarkable configurational stability. The calculated barriers to inversion and activation parameters (the values of which are collected in Tables 3 and 4) also suggest a subtle interplay of different mechanisms in the enantiomerization process. It was also observed that deprotonation does not take place in hexane with *s*BuLi in the absence of TMEDA. A model that highlights the role that either pre-lithiation or more reactive complexes may have on deprotonation reactions in hexane/TMEDA has been proposed.

Reactions in which stereochemistry is controlled have become invaluable tools for organic chemists. With reference to oxiranyllithiums, in particular, Yoshida and co-workers stated in a recent paper[30] that if the problems of decomposition and stereochemical isomerization related to such reactive intermediates "could be resolved, the utility of the oxiranyl anion methodology would be dramatically enhanced".

With regard to this, Yoshida and co-workers successfully overcame such issues by employing a flow microreactor system with efficient temperature control and short residence times. In this paper, we have shown for the first time that deprotonation of the above substituted styrene oxides in hexane/TMEDA at 183 K not only minimizes the carbene-like reactivity,[31] but also racemization, which whenever it occurs in THF, can mostly be blocked.

Table 3. Enantiomerization barriers and racemization half-lives of lithiated styrene oxides **1**,**2**,**4**,**5**,**9**,**10**-**Li** in THF, THF/TMEDA, and hexane.



Lithiated oxirane	R	Solvent	T [K]	TMEDA [equiv]	$\Delta G^{\neq}_{enant}$ [a] [kcal mol^{-1}]	$t_{1/2}$(rac)	σ [b]
1-**Li**	*m*-CF_3	THF	195	1	14.2	10.6 min	0.43
		THF	183	1	14.1	100.3 min	0.43
		THF	175	1	14.0	417.7 min	0.43
2-**Li**	*p*-CF_3	THF/Et_2O (3:2)	157	–	10.1	14 s	0.54
		THF	175	1	11.0	6 s	0.54
		hexane	183	1	14.0	91.1 min	0.54
4-**Li**	*o*-Cl	THF	195	–	14.0	5.8 min	–
		THF	190	–	13.8	11.2 min	–
		THF	175	–	13.7	185.9 min	–
		THF	195	1	14.0	6.8 min	–
		THF	183	1	13.9	55.8 min	–
		THF	175	1	13.8	287.3 min	–
5-**Li**	*m*-Cl	THF	195	–	14.4(8)	24.3 min	0.37 [c]
		THF	195	1	14.5(1)	26.4 min	0.37 [c]
9-**Li**	*o*-PhS	THF/Et_2O (3:2)	157	–	9.8	4 s	–
10-**Li**	*p*-PhS	THF	175	–	11.1	8 s	0.23 [d]

[a] The estimated error for all $\Delta G^{\neq}_{enant}$ values is ±0.1 kcal mol^{-1}. [b] Hammett σ constant (see ref. [26]). [c] For comparison, the Hammett σ constants for the *m*-F, *p*-F, and *p*-Cl substituents are 0.34, 0.06, and 0.23, respectively. In contrast to **4**-**Li** and **5**-**Li**, all the corresponding lithiated oxiranyllithiums proved to be configurationally stable in THF on the timescale of their reactions in the temperature range 175–195 K (see also ref. [11]). [d] For comparison, the Hammett σ constant for the *m*-PhS substituent is 0.15 (see also ref. [28]).

Table 4. Activation parameters for the enantiomerization of lithiated styrene oxides **1**-**Li** and **4**-**Li** in THF with or without TMEDA.

Lithiated oxirane	R	TMEDA [equiv]	$\Delta H^{\neq}_{enant}$ [kcal mol^{-1}]	$\Delta S^{\neq}_{enant}$ [cal mol^{-1} K^{-1}]
1-**Li**	*m*-CF_3	–	5.5 ± 0.5	−44 ± 1
		1	12.1 ± 0.5	−11 ± 3
4-**Li**	*o*-Cl	–	11.5 ± 0.5	−12 ± 3
		1	12.3 ± 0.2	−9 ± 1

To prove how this can be crucial to asymmetric synthesis, we have successfully prepared an industrially important antifungal agent ((*S*)-**16**) in a highly enantioenriched form (98:2 e.r.). In addition, the quest for "solvents in which race-

mization occurs only slowly", in the words of Haeffner et al.,[5c] could also be accomplished in the case of lithiated styrene oxides by carrying out their deprotonation reactions under certain experimental conditions (e.g., THF/TMEDA) and by modulating the temperature. This may also be of interest for establishing fruitful and efficient dynamic resolutions starting from racemic epoxides. This issue is currently being investigated in our laboratory.

Experimental Section

General: Tetrahydrofuran (THF), pentane, and hexane were freshly distilled under nitrogen, THF over sodium/benzophenone ketyl, and pentane and hexane over calcium hydride. For the ^{1}H and ^{13}C NMR spectra (^{1}H NMR: 600 MHz; ^{13}C NMR: 150 MHz, Bruker Avance 600), $CDCl_3$ was used as solvent. GC-MS analyses were performed on a HP 5890 gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Optical rotations were measured with a Perkin-Elmer 341 polarimeter using a cell of 1 dm pathlength at 25 °C; the concentration (*c*) is expressed in g/100 mL. Analytical thin-layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by using UV light (254 nm) or by spraying with a solution of 5 % (w/v) ammonium molybdate and 0.2 % (w/v) cerium(III) sulfate in 100 mL of a 17.6 % (w/v) aqueous solution of sulfuric acid and heating at 473 K for some time until blue spots appeared. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using the syringe/septum cap technique. Lithiation/deuteration reactions were performed in an ethanol/liquid N_2 (157 K), methanol/liquid N_2 (175 K), acetone/liquid N_2 (183 K), diethyl ether/dry ice (190 K), or acetone/dry ice (195 K) cold bath. The enantiomeric ratios were determined as follows: compound (*S*)-**16** by ^{1}H NMR analysis (600 MHz, $CDCl_3$) in the presence of the Mosher acid ((*R*)-(+)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoic acid;[32] molar ratio of the Mosher acid/**16**, 1:1), compounds **8**–**10** by HPLC analysis employing a Daicel Chiralcel OD-H column (250×4.6 mm), compounds **1**, **2**, **4**–**6, 11**, **12**, and **14** by HPLC analysis (HPLC: pump 1525, detector 996 PDA) employing a Cellulose Lux-2 column (250×4.6 mm), and compounds **3** and **7** by GC analysis (HP 6890) employing a Chirasil-DEX CB column (250×0.25 mm, column head pressure 18 psi, He flow 1.5 mL min^{-1}, oven temperature 100–110 °C). Racemic oxiranes were prepared by either the Corey–Chaykovsky epoxidation procedure[33] starting from the corresponding benzaldehyde derivatives (epoxides **2**, **4**–**8**, and **12**) or the methodology of Durst and co-workers[34] (epoxides **1** and **3**). The optically active epoxides **1**–**8** and **12** were synthesized as follows: compounds **2**, **4**–**7**, and **12** starting from the corresponding racemic mixtures by using Jacobsen and co-workers' hydrolytic kinetic resolution[35] and compounds **1**, **3**, and **8** starting from the corresponding α-chloro ketones[36] exploiting Noyori's asymmetric reduction. α-Chloro ketones were prepared from the commercially available acetophenone derivatives following reported procedures.[37] Racemic and optically active oxiranes **9**–**11** and **14** were prepared from racemic or optically active 4-(bromophenyl)oxiranes (**12**) according to previously reported procedures.[27] The spectroscopic data of epoxides **1**,[38] **2**,[38] **3**,[39] **4**,[35] **5**,[35] **6**,[35] **7**,[40] **8**,[41] **9**,[27] **10**,[27] **12**,[40] **14**[27] and of amino alcohol **16**[27] have been reported previously. For the spectroscopic data of compound **11** see the Supporting Information.

Kinetic studies: All the kinetic experiments were conducted in a closed vessel immersed in the appropriate cold bath for the temperature employed (see above). The temperatures were monitored by using a calibrated digital thermometer. The rate constants for the racemization of optically active oxiranylithiums were determined by plotting enantiomeric ratios against time after performing a series of lithiation/deuteration experiments on the corresponding epoxides at different temperatures and times as reported in the main text. Each point in the plot corresponds to a single experiment. The enantiomeric ratios determined at very short reaction times (less than 30 s, Table 2, Schemes 11 and 12) proved to be reproducible within the error limits of 5 %.

Lithiation/deuteration of optically active epoxides—general procedure: Standard solutions (0.05 M) of the respective optically active epoxide (0.1 mmol in 2 mL of dry solvent) and TMEDA (when required; 0.1 mmol) were cooled to the fixed temperature and treated with *s*BuLi (0.15 mmol, 1.3 M solution in cyclohexane) under N_2. After stirring the resulting mixture for the given time (see the main text and Supporting Information), MeOD (10 mmol) was added. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature, then diluted with brine (5 mL) and extracted with Et_2O (3×5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. The crude product was analyzed without further purification to determine the enantiomeric ratio as described above.

Acknowledgements

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