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Lithiated Fluorinated Styrene Oxides: Configurational Stability, Synthetic Applications, and Mechanistic Insight

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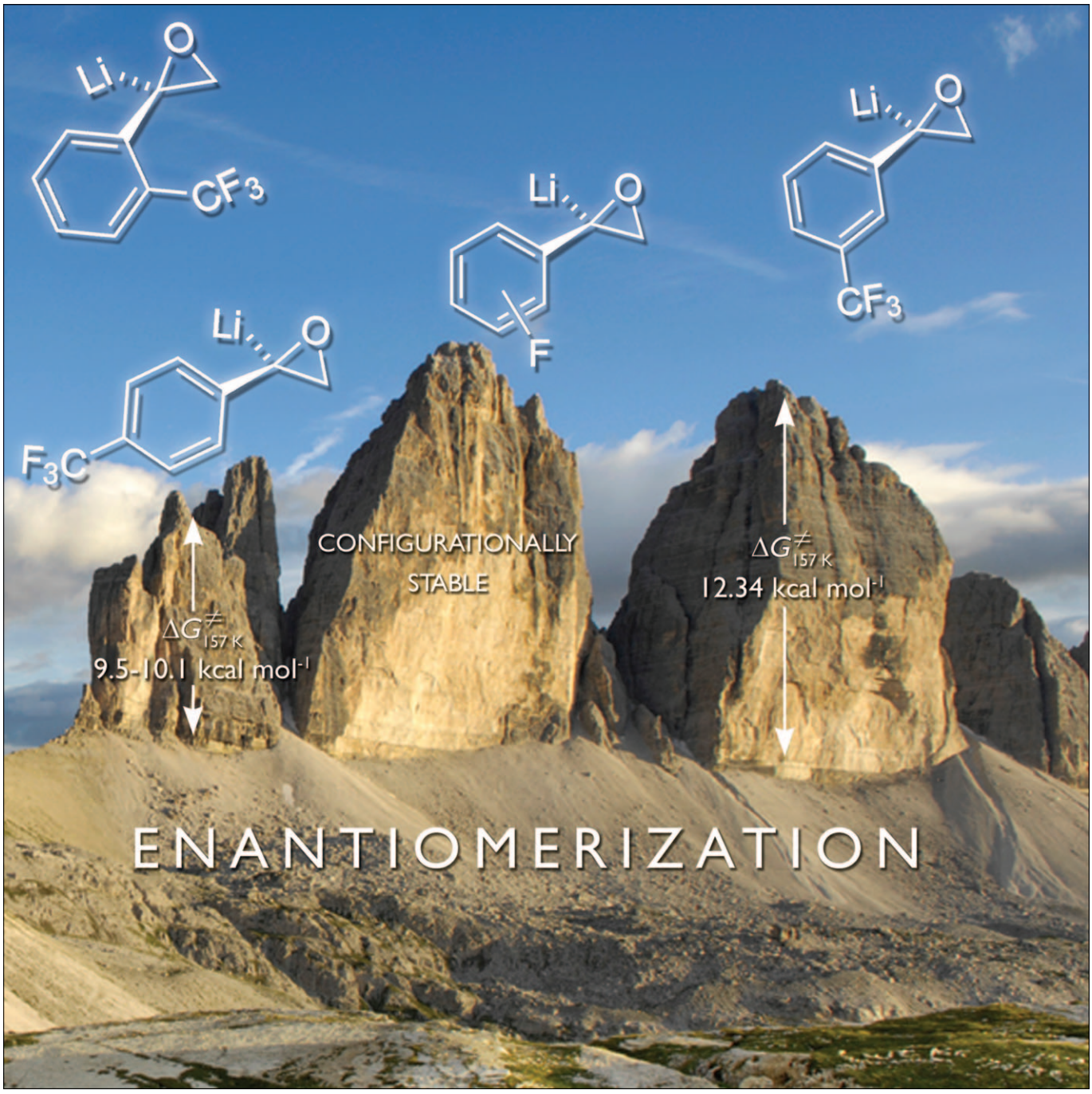
Dedicated to Professor José Barluenga on the occasion of his 70th birthday



Abstract: The configurational stability of some lithiated fluorinated styrene oxides has been investigated. Chemical studies have shown that in ethereal solvents α-lithiated *ortho*-, *meta*-, and *para*-fluorostyrene oxides (**2-Li**, α-**5-Li**, and α-**6-Li**) are all configurationally stable in the reaction time scale, whereas α-lithiated *ortho*-, *meta*-, and *para*-trifluoromethylstyrene oxides (**9-Li**, **13-Li**, and **14-Li**) are configurationally unstable. Optically active oxiranyllithiums **2-Li** and **9-Li**, could be stereospecifically generated and quenched with electrophiles. The corresponding derivatives were then successfully subjected to regiospecific ring-opening reactions with amines to give fluorinated β-amino alcohols with a stereodefined quaternary carbinol center, which are useful synthons in medicinal chemistry. The barriers of inversion have been calculated (Eyring equation) for oxiranyllithiums **9-Li**, **13-Li**, and **14-Li** by determining the enantiomeric ratios after electrophilic quenching on aging the enantioenriched organolithium for different times in THF; in the case of **9-Li**, activation parameters have also been determined. Mechanisms that may be responsible of the racemization oxiranyllithiums **9-Li**, **13-Li**, and **14-Li** undergo once generated are also discussed.

Keywords: amino alcohols · Eyring equation · fluorinated substituents · kinetics · oxiranyllithiums

Introduction

Fluorine holds a special place not only in the heart of the close-knit community of organic "fluorine chemists" but also in that of biologists, medicinal chemists, and people involved in the fields of materials and life sciences.[1] This is because the introduction of fluorine (which has unique steric and electronic properties),[2] as well as of fluorinated substituents in an organic molecule, can dramatically change its reactivity and/or modulate some biological activities such as physicochemical and pharmacokinetic properties,[3] and improve drug delivery.[4] The properties of fluorinated aromatic molecules have also made them suitable for widespread applications as agrochemicals, in particular, for modern crop protection and as insecticides, fungicides, and herbicides.[5] In addition, the employment of bioactive aromatic fluorinated compounds (whose availability in an optically pure form is still poor) is also challenging in biochemistry because of their potential chelating properties toward alkali and alkaline earth metal ions;[1d] thus, a stereocontrolled preparation of such compounds is of great interest.

α-Lithiated styrene and stilbene oxides are configurationally stable intermediates[6] and have been successfully employed as chiral synthons in asymmetric synthesis over the past few years.[7] With special reference to lithiated styrene oxide, a recent multinuclear magnetic resonance study, supported by density functional theory calculations, has been used to investigate its configurational stability as well as its dichotomic reactivity (carbanionic/carbene-like character), which has been related to the different aggregation states depending on the experimental conditions employed.[8] Optically active α-lithiated styrene oxide retains its absolute configuration when coupled in THF at 175 K with a large number of electrophiles. The stereochemical integrity is yet preserved in reactions with boronic esters in Et_2O at 158 K[9] but not in THF, thus suggesting that the stereochemical pathway of its trapping reactions surprisingly depends upon the solvent used, the temperature, and also the nature of the electrophile. As part of our recent studies aimed at investigating the substitution effect at the aryl group on the configurational stability of α-lithiated aryloxiranes, it has been quite recently reported that the *ortho*-positioned *para*-tolylsulfinyl group of α-lithiated styrene oxide induces, surprisingly, epimerization.[10] The influence of the sulfinyl group is remarkable not only from a stereochemical point of view but also considering the acidity enhancement occurring at the oxirane ring (in the presence of such a substituent) which could be lithiated, for the first time, also by lithium diisopropyl amide (LDA) at 195 K. Herein, we wish to report the effect of *ortho*-, *meta*-, and *para*-positioned fluorinated groups on the configurational stability of the corresponding lithiated derivatives, trapping reactions with electrophiles, and amine-promoted ring-opening reactions on the newly functionalized epoxides to give key synthons (such as chiral fluorinated aromatic β-aminoalcohols) having a stereogenic quaternary carbinol atom. In addition, for those lithiated intermediates proven to be configurationally unstable (*ortho*-, *meta*-, and *para*-trifluoromethyl derivatives) barriers to inversion and activation parameters have been calculated and discussed.

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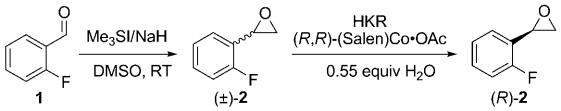
Supporting information for this article (^1H and ^{13}C NMR spectra for compounds **3b**,**c**, **4a**–**d**, **8**, and **10**) is available on the WWW under http://dx.doi.org/10.1002/chem.201000897.

Results and Discussion

Synthetic studies: Optically active *ortho*-fluorostyrene oxide (*R*)-**2** (Scheme 1) was prepared in two steps by the reaction of *ortho*-fluorobenzaldehyde **1** with dimethylsulfonium methylide in DMSO (Corey–Chaykovsky epoxidation)[11] at room temperature to give racemic epoxide (±)-**2** (70%

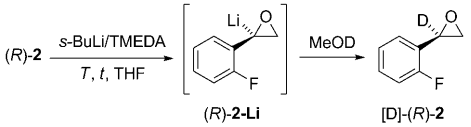
yield) followed by hydrolytic kinetic resolution (HKR) according to the Jacobsen[12] protocol (48 h, overall yield 18%) (Scheme 1).



Scheme 1.

Oxiranyllithium (*R*)-**2-Li** (Table 1) was smoothly generated by treatment of a precooled THF solution of (*R*)-**2** and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) with *s*BuLi.[13] Quenching the reaction mixture after 15 min with MeOD gave deuterated epoxide [D]-(*R*)-**2** (90% yield, 95% D) with complete retention of configuration of the starting oxirane (>98:2 enantiomeric ratio (e.r.)) (entry 1, Table 1).

Table 1. Lithiation–deuteration of (*R*)-**2**.



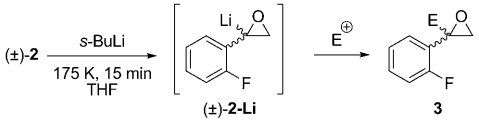
Entry	*T* [K]	*t* [min]	D [%][a]	Yield [%][b]	e.r.[c]
1	175	15	95	90	>98:2
2	175	180	95	10	>98:2
3	195	15	95	38	>98:2

[a] Calculated by ^{1}H NMR of the crude reaction mixture. [b] Isolated yield after column chromatography. [c] Enantiomeric ratio evaluated by chiral HPLC (see Experimental Section).

This fact proves that (*R*)-**2-Li** is configurationally stable[14] at least on the time scale of its generation and addition to an electrophile at 175 K. The chemical and configurational stabilities of (*R*)-**2-Li** were also checked at longer reaction times. After stirring the above reaction mixture for 180 min at 175 K and quenching with MeOD, [D]-(*R*)-**2** was recovered with 95% D and, again, with the configuration at the benzylic-type carbon unaffected (>98:2 e.r.); however, the isolated yield after column chromatography was only 10% (entry 2, Table 1). A careful inspection of the crude product revealed a complex mixture of products (mainly enediols and alkenes), most probably originating by the reported "eliminative dimerization" and "reductive alkylation" processes.[15] Therefore, oxiranyllithium (*R*)-**2-Li**, at longer reaction time, decomposes rather than racemizes. This behavior is in line with that found for other α-lithiated aryloxiranes.[6] A higher temperature than 175 K favored the carbenoid nature of (*R*)-**2-Li** as well; indeed, after only 15 min stirring at 195 K, followed by quenching with MeOD, [D]-(*R*)-**2** was again isolated in poor yield (38%, entry 3, Table 1) although with high deuterium incorporation (95% D) and high e.r. (>98:2). It is worth noting that comparable yields and deuterium incorporation were similarly obtained at variable times (15 min: 95% D and 90% yield; 180 min: 95% D and 10% yield) deprotonating (*R*)-**2** with *s*BuLi in the absence of TMEDA, which, therefore, does not act in this case as a modifier of *s*BuLi reactivity.

The nucleophilicity of (*R*)-**2-Li** toward other electrophiles was then investigated. The reactions with MeI, Me_3SiCl, and acetone occurred smoothly, leading to the corresponding α,α-disubstituted epoxides **3a–c** in moderate to good yields (entries 1–3, Table 2).

Table 2. Synthesis of α,α-disubstituted *ortho*-fluorostyrene oxides **3**.

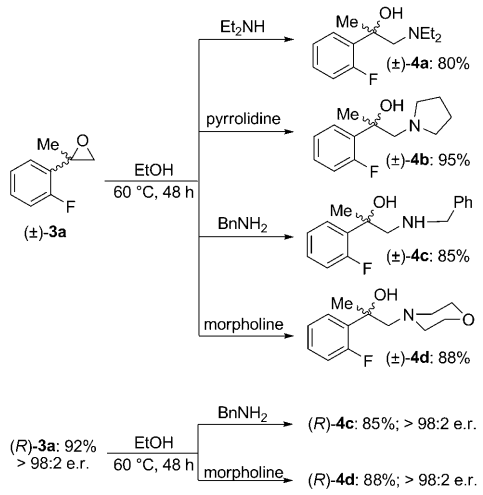


Entry	Electrophile	Epoxide **3** (yield [%])[a]
1	MeI	**3a** (90)
2	Me_3SiCl	**3b** (40)
3	$(CH_3)_2CO$	**3c** (57)

[a] Isolated yield after column chromatography.

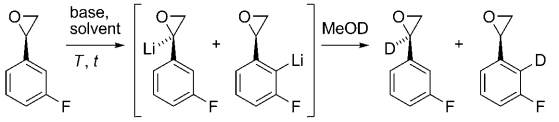
With terminal epoxides **3a–c** in hand, we reasoned they could represent useful synthons for the preparation of fluorinated β-aminoalcohols (Scheme 2). Epoxide **3a** was used as a probe. Dissolving **3a** in EtOH followed by treatment with diethylamine, pyrrolidine, benzylamine and morpholine at 60°C for 48 h, resulted in the highly regioselective formation of the corresponding β-aminoalcohols **4a–d** in very good yields (80–95%, Scheme 2). Similarly, starting from enantioenriched epoxide (*R*)-**3a** (prepared in 92% yield and > 98:2 e.r. by quenching (*R*)-**2-Li** with MeI), it was possible to prepare highly enantioenriched (> 98:2 e.r.) β-aminoalcohols (*R*)-**4c** (85% yield) and (*R*)-**4d** (88% yield) (Scheme 2). Such fluorinated phenylpropanolamines have recently attracted considerable interest either as agrochemical bioregulators or as agonists on octopamine receptors in cockroach ventral nerve cords.[16] A microwave-assisted synthesis of *N*-substituted indoles which exploits an amine-promoted epoxide ring-opening reaction of *ortho*-fluoro-substituted styrene oxides has also been reported.[17]

In principle, fluoro-substituted styrene oxides would have three types of centers capable of being lithiated: the benzylic position and the sites *ortho* to the fluorine substituent and to the oxiranyl ring. A fluorine atom itself, however, occupies a very low position in the hierarchy of directed *ortho* metalation (DoM) groups.[18] Therefore, the fact that *ortho*-fluorostyrene oxide undergoes a highly regioselective benzylic lithiation when treated with *s*BuLi/THF may most probably be the result of the synergistic cooperation of an oxiranyl-driven complex-induced proximity effect[8a] and a fluorine-promoted electron-withdrawing inductive effect; that is, the benzylic hydrogen atom in **2** is more acidic than the hydrogen atom *ortho* to fluorine.[19] Optically active *meta*-fluorostyrene oxide (*R*)-**5** (Table 3) (>98:2 e.r.) was



Scheme 2.

Table 3. Lithiation–deuteration of *meta*-fluorostyrene oxide (*R*)-**5**.



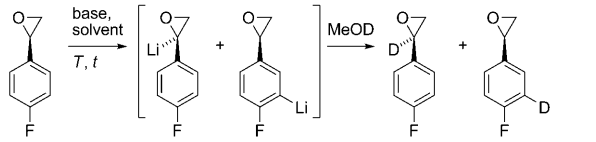
Entry	Base	Solvent	T [K]	t [min]	[D]-(*R*)-α-**5**[a]	[D]-(*R*)-*o*-**5**[a]
1	*s*BuLi	THF	195	0.5	30	50
2	*s*BuLi	Et_2O	175	10	[b]	[b]
3	*s*BuLi	hexane	183	10	–[c]	–[c]
4	*s*BuLi/ TMEDA	hexane	183	5	30	70
5	LDA/*t*BuOK	THF	175	30	–	15
6	*n*BuLi (1 equiv)	THF	175	10	<2	60
7	*n*BuLi (3 equiv)	THF	175	10	5	85

[a] Evaluated by ^{1}H NMR analysis of the crude reaction mixture. [b] Complex mixture. [c] No deprotonation occurred.

prepared by HKR of the corresponding racemic epoxide (see Experimental). Deprotonation with *s*BuLi in THF at 195 K and quenching with a deuterium source after 30 s afforded (^{1}H NMR analysis) [D]-(*R*)-*ortho*-**5** (50%) from (*R*)-*ortho*-**5-Li** and [D]-(*R*)-α-**5** (30%) from (*R*)-α-**5-Li**; about 20% of **5** remained unreacted (entry 1, Table 3). The mixture of the two deuterated compounds, [D]-(*R*)-α-**5** and [D]-(*R*)-*ortho*-**5**, once isolated by column chromatography, turned out to be highly enantiomerically enriched with the configuration at the benzylic stereogenic centers unaffected (>98:2 e.r., GC analysis, see Experimental Section). A number of bases and parameters were also screened (entries 1–7, Table 3). With respect to this, it is worth noting that: *t*BuLi and lithium diisopropylamide (LDA) were ineffective, a mixture of *s*BuLi/TMEDA in hexane gave a mixture of [D]-(*R*)-*ortho*-**5** and [D]-(*R*)-α-**5** in a 70:30 ratio (entry 4, Table 3)[20] that raised up to 85:5 employing 3 equiv of *n*BuLi (entry 7, Table 3).

By contrast, lithiation of optically active *para*-fluorostyrene oxide (*R*)-**6** with *s*BuLi (2 equiv, THF, 175 K, 15 min) (see Experimental Section) took place mainly at the benzylic position to give, after MeOD quenching, [D]-(*R*)-α-**6** in 70% and [D]-(*R*)-*ortho*-**6** in 20% yield, the remaining 10% being unreacted starting epoxide (^{1}H NMR analysis of the crude reaction mixture) (entry 1, Table 4).

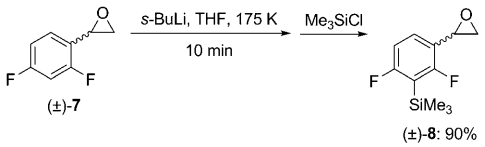
Table 4. Lithiation–deuteration of *para*-fluorostyrene oxide (*R*)-**6**.



Entry	Base	Solvent	T [K]	t [min]	[D]-(*R*)-α-**6** [%][a]	[D]-(*R*)-*o*-**6** [%][a]
1	*s*BuLi	THF	175	10	70	20
2	*s*BuLi/ TMEDA[b]	hexane	183	10	70	20
3	LDA/ *t*BuOK	THF	175	30	–	30

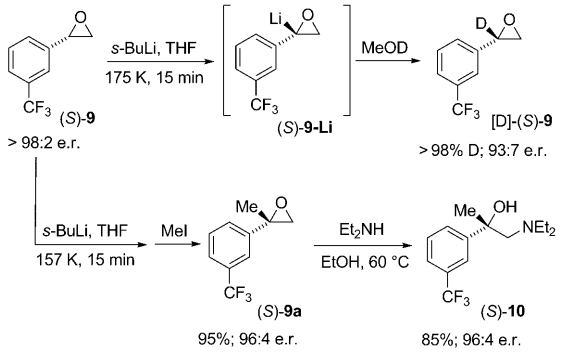
[a] Calculated by ^{1}H NMR. [b] Lithiation performed in the presence of 3 equiv of TMEDA.

However, the isolation by column chromatography of the mixture of deuterated compounds, [D]-(*R*)-α-**6** and [D]-(*R*)-*ortho*-**6**, confirmed that no racemization occurred at the benzylic position. α-Lithiated *para*-fluorostyrene oxide (*R*)-α-**6-Li** was shown to be configurationally stable up to a reaction time of 90 min. The use of the *s*BuLi/TMEDA complex in hexane at 183 K gave results similar to those obtained with *s*BuLi in THF (entry 2, Table 4), whereas the mixture LDA/*t*BuOK furnished only [D]-(*R*)-*ortho*-**6** in 30% yield (THF, 175 K, 30 min), the remaining being unreacted starting epoxide (entry 3, Table 4). Other metalating agents such as LDA and lithium 2,2,6,6-tetramethylpiperidide were ineffective (THF, 175 K, 30 min). Lithiation of compound **7** (Scheme 3), bearing two fluorine atoms in a *meta* orientation, with *s*BuLi (THF, 175 K), followed by quenching with Me_3SiCl after 15 min, gave adduct **8** in almost quantitative yield after column chromatography (Scheme 3). Most likely, in this case, the regioselectivity of lithiation is achieved by cooperation of both complexation and inductive effects.



Scheme 3.

Attention was next turned to investigating lithiation of *ortho*-, *meta*-, and *para*-trifluoromethyl-substituted derivatives. Optically active *meta*-trifluoromethylstyrene oxide (*S*)-**9** (>98:2 e.r.) (see Experimental Section), when treated with *s*BuLi (THF, 175 K, 15 min), could be quantitatively α-deprotonated to give only (*S*)-**9-Li** so furnishing, after quenching with MeOD, [D]-(*S*)-**9** (>98% D) with 93:7 e.r. (Scheme 4). This result is in line with the fact that the trifluoromethyl substituent, in spite of being a strong electron-withdrawing group, is, however, a weaker DoM activator than the fluorine atom itself.[21] Lowering the temperature to 157 K, (*S*)-**9-Li** could be quenched with MeI after 15 min to give (*S*)-**9a** (Scheme 4) in 95% yield and 96:4 e.r. The latter was subjected to a ring-opening reaction with Et_2NH to give aminoalcohol (*S*)-**10** in 85% isolated yield and 96:4 e.r. However, no deprotonation occurred when (*S*)-**9** was treated with *s*BuLi employing hexane or Et_2O as the solvent. Therefore, unlike lithiated *ortho*-, *meta*-, and *para*-fluorostyrene oxides, which are configurationally stable on the time scale of the reaction, (*S*)-**9-Li** in part loses its original configurational integrity (93:7 e.r. at 175 K and 96:4 e.r. at 157 K).



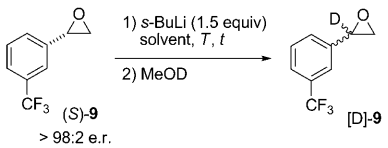
Scheme 4.

Thus, we found it instructive to study in detail the kinetics of the racemization of (*S*)-**9-Li** in THF as well as that of lithiated *ortho*- and *para*-trifluoromethylstyrene oxides (which were shown to be configurationally unstable in THF (see below)), especially because a knowledge of the stereochemical stability and the rate of interconversion of chiral organolithiums is critical to asymmetric substitution chemistry as well as for dynamic kinetic/thermodynamic resolutions.

Kinetic studies: The approximate racemization half-life of configurationally unstable lithiated styrene oxides was in all cases determined by performing deprotonation/quenching experiments with a deuterium source.

meta-Trifluoromethylstyrene oxide (*S*)-**9** (>98:2 e.r.) was first deprotonated at 195 K with *s*BuLi (1.5 equiv) in THF for a time *t* followed by MeOD quench. The recovered epoxide was then analyzed, each time, by a chiral stationary phase HPLC to calculate its e.r. (Table 5). As expected (see discussion above), racemization of (*S*)-**9-Li** was found to proceed slowly and, at 195 K, [D]-**9** was recovered with 71:29–54:46 e.r. between 3 and 20 min (entries 1–5, Table 3), each time with >98% D (evaluated by ^{1}H NMR analysis of the crude reaction mixture). The plot of $\ln(|2X_R(\mathbf{9})-1|)$ versus *t* showed a very good linear relationship ($R^2=0.993$) and was found to obey strictly the kinetics of first-order racemization;[22] the slope, corresponding to $-k_{rac}$, indicated an estimated half-life of racemization, $t_{1/2}$, of 7.2 min at 195 K (Figure 1). Application of the Eyring equation[23] to the estimated k_{enant} (calculated as $k_{rac}/2$), for the oxiranyllithium (*S*)-**9-Li** indicates a barrier to inversion ($\Delta G^{\neq}$ (enant)) of 14.01 ± 0.04 kcal mol^{-1} at 195 K in THF.

Table 5. Lithiation-deuteration of *meta*-trifluoromethylstyrene oxide (*S*)-**9** at different temperatures and times.



Entry	*T* [K]	Solvent	*t* [min]	e.r.[a]
1	195	THF	3	71:29
2	195	THF	5	68:32
3	195	THF	10	61:39
4	195	THF	15	58:42
5	195	THF	20	54:46
6	175	THF	15	93:7
7	175	THF	30	85:15
8	175	THF	40	80:20
9	175	THF	60	71:29
10	157	THF/Et_2O 3:2	20	97:3
11	157	THF/Et_2O 3:2	30	95:5
12	157	THF/Et_2O 3:2	40	94:6
13	157	THF/Et_2O 3:2	60	92:8

[a] Determined by chiral stationary phase HPLC.

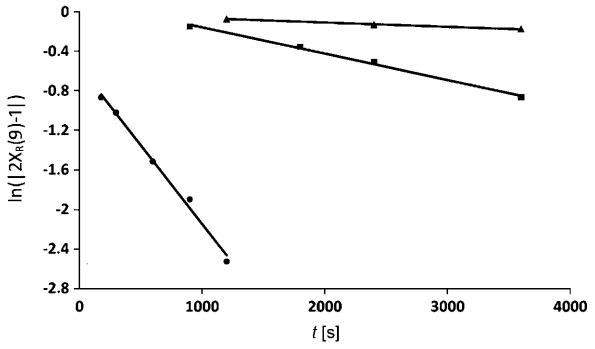


Figure 1. Plot of $\ln(|2X_R(\mathbf{9})-1|)$ vs delay time at different temperatures (157 ▲, 175 ■, and 195 K ●) in lithiation–deuteration exchange on (*S*)-**9**: estimation of the racemization half-life of the oxiranyllithium (*S*)-**9-Li**. All reactions run at [(*S*)-**9**] = 0.05 M. $X_R(\mathbf{9})$ is the mole fraction of (*R*)-**9**, and $|2X_R(\mathbf{9})-1|$ is equivalent to the % *ee* of **9** expressed as a number between 0 and 1. T = 157 K, $k_{rac} = 4.24\times10^{-5}$ s^{-1}, $t_{1/2}$ = 272.4 min, R^2 = 0.998, $\Delta G^{\neq}$ (enant) = 12.34 ± 0.03 kcal mol^{-1}; T = 175 K, $k_{rac} = 2.70\times10^{-4}$ s^{-1}, $t_{1/2}$ = 43.4 min, R^2 = 0.995, $\Delta G^{\neq}$ (enant) = 13.16 ± 0.04 kcal mol^{-1}; T = 195 K, $k_{rac} = 1.59\times10^{-3}$ s^{-1}, $t_{1/2}$ = 7.2 min, R^2 = 0.993 , $\Delta G^{\neq}$ (enant) = 14.01 ± 0.04 kcal mol^{-1}.

Similar deprotonation/deuteration experiments were also carried out on (*S*)-**9** after lowering the temperature to 175 and 157 K (Table 5). At longer reaction times (15–60 min), [D]-(*S*)-**9** was recovered with ever increasing e.r. ranging from 93:7–71:29 (175 K) (entries 6–9, Table 5) to 97:3–92:8 (157 K) (entries 10–13, Table 5). The plot of $\ln(|2X_R(\mathbf{9})-1|)$ versus t appeared, again, linear ($R^2=0.993$ and 0.998) and the first-order racemization kinetics indicated an estimated racemization $t_{1/2}$ of 43.4 and 272.4 min corresponding to enantiomerization barriers $\Delta G^{\neq}$ (enant) of 13.16 ± 0.04 and 12.34 ± 0.03 kcal mol^{-1} at 175 and 157 K, respectively (at 195 K: $t_{1/2}$ = 7.2 min, $\Delta G^{\neq}$ (enant) = 14.01 ± 0.04 kcal mol^{-1}).

From these studies, activation parameters for the enantiomerization of (*S*)-**9-Li** could then be determined. To this end, the above free energies of enantiomerization were plotted as a function of temperature (Figure 2). A very good relationship was found ($R^2=0.999$), corresponding to an enthalpy of activation ($\Delta H^{\neq}$) of 5.45 ± 0.13 kcal mol^{-1} and an entropy of activation ($\Delta S^{\neq}$) of -43.92 ± 0.75 cal mol^{-1} K^{-1}.

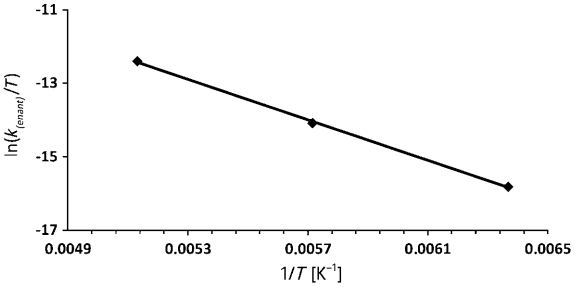
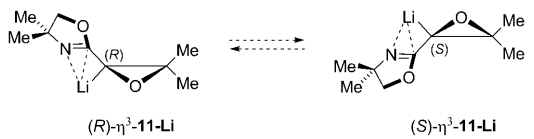


Figure 2. Eyring plot and activation parameters for enantiomerization of (*S*)-**9-Li**.

The measured small enthalpy of activation along with a strong negative entropy of activation are both consistent with either additional solvation of the transition state or formation of a larger dipole resulting in electrostatic restriction of the solvent.[24] Therefore, in this case, the transformation of a contact ion pair into a solvent-separated ion pair (SSIP)[25] may be conceived as the rate-determining step.

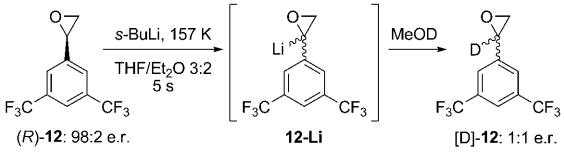
However, epimerization through a higher aggregate cannot be ruled out.[26] In the case of 1-lithio-1-phenyl-2,2-dimethylcyclopropane (which exhibits a topomerization barrier markedly lower than that of the configurationally stable cyclopropyllithium), for example, the large negative activation entropy (ca. -32 cal mol^{-1} K^{-1})) points toward just the participation of aggregate structures.[27] As an additional example, it is worth noting that in contrast to α-lithiated aryloxiranes, which are usually configurationally stable (with the restriction discussed above), α-lithiated oxazolinyloxiranes are not; the bias that lithium has to be strongly coordinated by the iminic oxazoline moiety was found to be a crucial factor in causing a fast racemization for the latter lithium carbenoids. In particular, in the case of 1-lithio-1-(2-oxazolinyl)-2,2-dimethyloxirane **11** (Scheme 5), the estimated inversion barrier $\Delta G^{\neq}$ (enant) was 8.8 kcal mol^{-1} (143 K, 3:2 THF/Et_2O): an indirect dynamic interconversion mediated by higher aggregates between two lithiated η^3-aza-allyl enantiomeric monomers has been proposed[28] and an inverting tetrahedral configuration is very likely to take place rather than an inverting planar configuration.



Scheme 5. Indirect dynamic interconversion between the two lithiated η^3-aza-allyl enantiomeric monomers (*R*)- and (*S*)-η^3-**11-Li**.

To prove that, (*S*)-**9** was also deprotonated with *s*BuLi in THF but at a higher concentration (0.5 M vs 0.05 M) to favor the formation of higher aggregates, if any. Surprisingly, after quenching the mixture with MeOD, 30 min being the reaction time, [D]-(*S*)-**9** was recovered with 98% D and the same e.r. (85:15) obtained in the case of the reaction run at a lower (0.05 M) concentration, although the amount of byproducts in the crude mixture (mainly alkenes and enediols) increased to about 20% in the former case. Most probably, as observed for lithiated styrene oxide,[8a] at a higher concentration, (*S*)-**9-Li** may be similarly more prone to self-associate to give higher aggregates with a more pronounced "carbene-like" reactivity.

3,5-Bis(trifluoromethyl)styrene oxide (*R*)-**12** (98:2 e.r.) was prepared by means of Noyori's asymmetric reduction of the corresponding α-chloroketone (see Experimental Section).[29] After treating (*R*)-**12** with *s*BuLi (1.5 equiv) in THF/Et_2O (3:2), followed by quenching with MeOD, completely racemic [D]-**12** was recovered (90% yield and 89% D) even at 157 K after a reaction time of 5 s (Scheme 6).



Scheme 6.

The trifluoromethyl group is known to be one of the most powerful electron-withdrawing groups in structural organic chemistry.[30] Thus, the presence of two such groups in a *meta* orientation is most probably enough to lead to the SSIP directly on deprotonation, thereby allowing anion **12-Li** to be configurationally unstable.

We then turned to *ortho*-trifluoromethylstyrene oxide (*R*)-**13** (>98:2 e.r., see Experimental Section (Table 6); it was similarly investigated by deprotonation/deuteration sequences at variable times with *s*BuLi (1.5 equiv) in THF/Et_2O (3:2). As shown in Table 6 (entries 1–4), only after a 3 s deprotonation time at 157 K, the addition of MeOD es-

sentially gave racemic [D]-**13**. This is consistent with a configurational instability of **13-Li**, which undergoes racemization even faster than **9-Li**. Eyring analysis of the data (Figure 3) gave a racemization half-life of 1.6 s at 157 K ($R^2=0.9953$), corresponding to an inversion barrier $\Delta G^{\neq}$ (enant) of 9.46 ± 0.01 kcal mol^{-1}.

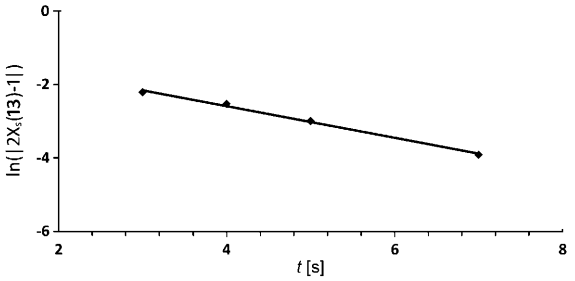
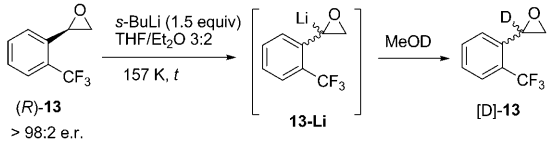


Figure 3. Plot of $\ln(|2X_s(\mathbf{13})-1|)$ vs delay time at 157 K in lithiation–deuteration exchange on (*R*)-**13**: estimation of the racemization half-life of the oxiranyllithium **13-Li**. All reactions run at [(*R*)-**13**] = 0.05 M. k_{rac} = 0.434 s^{-1}, $t_{1/2}$ = 1.6 s, R^2 = 0.9953, $\Delta G^{\neq}$ (enant) = 9.46 ± 0.01 kcal mol^{-1}.

Table 6. Lithiation–deuteration of *ortho*-trifluoromethylstyrene oxide (*R*)-**13** at different times at 157 K.

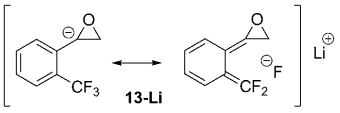


entry	*t* [s]	e.r.[a]	% D[b]
1	3	56:44	84
2	4	54:46	85
3	5	53:47	92
4	7	51:49	95

[a] Determined by chiral stationary phase HPLC and corrected for the percent deuterium found. [b] Evaluated by ^{1}H NMR analysis of the crude reaction mixture.

At lower temperatures than 157 K and at very short reaction times (less than 10 s), the kinetics of deprotonation competes with that of racemization, thereby rendering the calculation of activation parameters for this lithiated system impractical.

The lower inversion barrier found for **13-Li** compared with **9-Li** raises the possibility that an alternative or cooperative mechanism is under way for racemization of the former oxiranyllithium other than those discussed above. Actually, if one looks at the lithiated system **13-Li**, the close spatial proximity of lithium to the *ortho*-trifluoromethyl group opens the opportunity for an intramolecular coordination of lithium to such a group. Organic fluorine can be, indeed, regarded as an efficient donor atom in the coordination of both alkali and alkaline earth metal ions.[1d,31] In our case, one possibility is that fluorine may really be involved in promoting what is usually called a "conducted tour"-type mechanism in which the lithium is "escorted" from one face to the other face of the oxiranyllithium.[32] However, it is worth pointing out that, in general, although internal coordination is often known to influence the barrier for interconversion at a stereogenic lithiated carbon atom, it is not always predictable whether such an interconversion will be faster or slower.[33,34] Alternatively, for anions such as **13-Li**, one could also think of a plausible carbon–fluorine no-bond resonance (hyperconjugation) as a stabilizing mesomeric mechanism (Scheme 7).



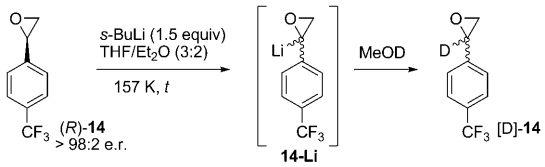
Scheme 7. Carbon–fluorine no-bond resonance in lithiated oxiranyllithium **13-Li**.

Indeed, fluorine hyperconjugation has frequently been invoked for interpreting various bond lengths and solvolytic reactivities of polyhalogenated compounds.[35] However, relying on the ^{13}C NMR resonances of C-*ortho* and C-*para* phenyl as a criterion for ascertaining effective (or no) delocalization of the π-charge into the phenyl ring,[8a,25a] preliminary NMR investigations on **13-Li**[34] indicate that such carbons were shifted upfield with respect to those of the neutral **13** (falling at 128.0–129.0 ppm) by about 10 ppm only. This would be consistent with a negligible transfer of the carbanion charge into the phenyl π-system as similarly observed in lithiated styrene oxide.[8a] C–F anionic hyperconjugation has also been found not to play a significant role in the stabilization of other trifluoromethyl anion derivatives.[36]

Finally, the configurational stability of α-lithiated *para*-trifluoromethyl-substituted styrene oxide **14-Li** (Table 7) was also investigated.

Lithiation (*s*BuLi, 1.5 equiv) of optically active (*R*)-**14** (> 98:2 e.r.) (Table 7) (see Experimental Section) at 157 K (THF/Et_2O 3:2), followed by electrophilic quenching with

Table 7. Lithiation–deuteration of *para*-trifluoromethylstyrene oxide (*R*)-**14** at different times at 157 K.



Entry	*t* [s]	e.r.[a]	% D[b]
1	5	67:33	64
2	10	61:39	75
3	20	57:43	83
4	30	53:47	88

[a] Determined by chiral stationary phase HPLC and corrected for the percent deuterium found. [b] Evaluated by ^{1}H NMR analysis of the crude reaction mixture.

MeOD on aging the enantioenriched organolithium for different times (Table 7), proved that **14-Li**, similarly to **13-Li**, is configurationally unstable; indeed, the e.r. of the corresponding deuterated [D]-**14** dropped back to 67:33 soon after 5 s. The activation free energy for enantiomerization $\Delta G^{\neq}$ (enant) of **14-Li**, calculated from the corresponding Eyring plot ($R^2 = 0.9812$) (Figure 4) was 10.13 ± 0.03 kcal mol^{-1} at 157 K, which gives a $t_{1/2}$ (rac) of 13.5 s.

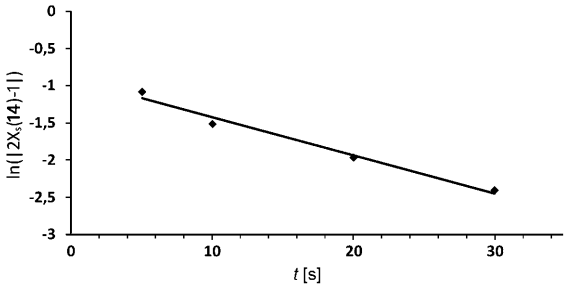


Figure 4. Plot of $\ln(|2X_S(\mathbf{14})-1|)$ vs delay time at 157 K in lithiation–deuteration exchange on (*R*)-**14**: estimation of the racemization half-life of the oxiranyllithium **14-Li**. All reactions run at [(*R*)-**14**] = 0.05 M. k_{rac} = 0.0512 s^{-1}, $t_{1/2}$ = 13.5 s, R^2 = 0.9812, $\Delta G^{\neq}$ (enant) = 10.13 ± 0.03 kcal mol^{-1}.

Conclusion

In conclusion, a study on the configurational stability of some lithiated fluorinated styrene oxides has been carried out. α-Lithiated *ortho*-, *meta*-, and *para*-fluorostyrene oxides (**2-Li**, α-**5-Li**, and α-**6-Li**) were all shown to be configurationally stable. Optically active oxiranyllithium (*R*)-**2-Li**, in particular, could be deprotonated and stereospecifically quenched with some electrophiles. Then, the corresponding functionalized derivatives so obtained were successfully subjected to regiospecific ring-opening reactions with amines to give fluorinated β-aminoalcohols having a stereodefined quaternary carbinol center. In the case of the *meta*- and *para*-fluorinated derivatives (**5** and **6**), benzylic lithiation competes to a variable extent with *ortho*-lithiation to the fluoro-adjacent position depending on the base and the solvent used. In contrast, α-lithiated *ortho*-, *meta*-, and *para*-trifluoromethylstyrene oxides (**9-Li**, **13-Li**, and **14-Li**) proven to be configurationally unstable. Among them, optically active lithiated *meta*-trifluoromethylstyrene oxide (*S*)-**9-Li** racemizes much slower than the corresponding *ortho*- and *para*-isomers **13-Li** and **14-Li**. However, when two trifluoromethyl groups are in a *meta* orientation to each other, as in the case of (*R*)-**12**, the corresponding anion **12-Li** undergoes a very fast racemization thus showing a configurational instability. The barriers to inversion were calculated for oxiranyllithiums **9-Li**, **13-Li**, and **14-Li** and, in the case of **9-Li**, also activation parameters. Most likely, strong inductive field effects provided by a group such as the trifluoromethyl group may play a major role in stabilizing all of the above regioisomeric benzylic-type oxiranyllithiums, thereby promoting racemization at a rate that is dependent on the relative position of the CF_3 group on the phenyl ring. With regard to that, it is of interest to observe that the barriers to inversion in the case of lithiated *meta*- and *para*-trifluoromethylstyrene oxides **9-Li** (12.34 kcal mol^{-1} at 157 K) and **14-Li** (10.13 kcal mol^{-1} at 157 K) parallel those of σ_m and σ_p of the CF_3 group, which are 0.43 and 0.53, respectively; that is, a lower barrier value corresponds to a higher Hammett σ value. Lithiated *meta*- and *para*-fluorostyrene oxides **5-Li** and **6-Li**, which are both configurationally stable, do have the lowest Hammett σ values, that is 0.34 and 0.06, respectively. In the case of lithiated *ortho*-trifluoromethylstyrene oxide **13-Li**, a possible synergistic cooperation of another competing mechanism, such as a "conducted tour" mechanism, may justify the lowest activation free energy found for racemization (9.46 kcal mol^{-1} at 157 K).

The calculation of the barriers to inversion for such oxiranyllithiums, the intimate knowledge of their racemization mechanisms, and the possibility of slowing down their rate of interconversion in the presence of ligands or different solvents, is quite interesting for setting up either stereoselective synthesis of interesting target molecules or useful and efficient dynamic resolutions. These issues will be subject of future investigations.

Experimental Section

General: Tetrahydrofuran (THF) was freshly distilled under a nitrogen atmosphere over sodium/benzophenone. Petroleum ether refers to the 40–60 °C boiling fraction. For the ^{1}H, ^{13}C and ^{19}F NMR spectra (^{1}H NMR 400, 600 MHz; ^{13}C NMR 150 MHz; ^{19}F NMR 376 MHz), $CDCl_3$ was used as the solvent. ^{19}F NMR spectra were recorded using trichlorofluoromethane ($CFCl_3$) as an internal standard ($\delta = 0$ ppm). GC-MS spectrometry analyses were performed on a gas chromatograph (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Optical rotation was measured with a polarimeter using a cell of 1 dm path length at 25 °C; the concentration (*c*) is expressed in g per 100 mL. Melting points were uncorrected. Elemental analyses were performed by using a Carlo Erba CHNS-O EA1108-Elemental Analyzer. Analytical thin-layer chromatography (TLC) was carried out on precoated 0.25 mm thick plates of Kieselgel 60 F254; visualization was accomplished by 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 17.6% (w/v) aq. sulphuric acid and heating to 200 °C for some time until blue spots appear. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique. Lithiation-deuteration reactions were performed using an ethanol/liquid N_2 (157 K) or methanol/liquid N_2 (175 K) or acetone/dry ice (195 K) cold bath. The enantiomeric ratios were determined as follows: compound (*S*)-**10**, by ^{1}H NMR analysis (600 MHz, CCl_4 with [D_4]MeOH as the external standard) in the presence of the Chiral Solvating Agent (CSA) (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol,[37] (CSA/(**10**) molar ratio 2:1); compounds **4c**,**d**, by HPLC analysis employing a Daicel Chiralcel OD-H column (250 × 4.6 mm); compounds **5**, **9**, **9a**, and **14**, by HPLC analysis employing a Cellulose Lux-2 column (250 × 4.6 mm); compounds **2**, **3a**, **6**, and **13**, by GC analysis 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 either according to the Corey–Chaykovsky[11] epoxidation procedure starting from the corresponding benzaldehyde derivatives (epoxides **2**, **5**, **6**, and **14**) or according to Durst[38] methodology (epoxides **9** and **13**). The following optically active epoxides were synthesized as follows: compounds **2**, **5**, and **14** starting from the corresponding

racemic mixtures by using the Jacobsen hydrolytic kinetic resolution,[12] whereas compounds **9**, **12**, and **13** starting from the corresponding α-chloroketones exploiting the Noyori asymmetric reduction.[29] α-Chloroketones were prepared from the commercially available acetophenone derivatives, likewise as reported.[39] (*R*)-(α)-4-Fluorostyrene oxide **6** (99.5:0.5 e.r.) is commercially available. Spectroscopic data of compounds **2**,[40] **3a**,[17] **5**,[40] **7**,[41] **9**,[42] **9a**,[42] **12**,[43] **13**,[42] and **14**[42] have been reported.

Kinetic studies: All kinetics experiments were conducted in a closed vessel immersed in a given cold bath according to the temperature employed (see above). The temperature was monitored using a calibrated digital thermometer. The rate constants for the racemization of optically active oxiranylithiums (*S*)-**9-Li**, (*R*)-**13-Li** and (*R*)-**14-Li** were determined by plotting enantiomeric ratios over time after performing a series of lithiation–deuteration experiments on the corresponding epoxides (*S*)-**9**, (*R*)-**13** and (*R*)-**14** at different temperatures and times as reported in the main text. Each point in the plot corresponds to a single experiment. The detected enantiomeric ratios at very short reaction times (less than 30 s, Tables 6 and 7) proven to be reproducible within the limits of 5% of the stated ratio.

Lithiation–deuteration sequence on epoxides (*S*)-9, (*R*)-12, (*R*)-13 and (*R*)-14—General kinetic run: Standard solutions (0.05 M) of the respective optically active epoxide (0.1 mmol in 2 mL of dry THF for reactions performed at 175 K or 195 K and of dry THF/Et_2O 3:2 for reactions performed at 157 K) were prepared and treated with *s*BuLi (0.15 mmol, 1.3 M solution in cyclohexane) under N_2. After stirring the resulting mixture for the measured time period (see Tables 5–7), MeOD (10 mmol) was added all at once. 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 with Na_2SO_4 and concentrated in vacuo. The crude product was analyzed without further purification to check the enantiomeric ratio as described above.

Synthesis of epoxides 3a-c, 8 and 9a—General procedure: A solution of epoxide **2**, **7** or **9** (0.5 mmol) in dry THF (5 mL) was treated at 175 K and under N_2 with *s*BuLi (0.6 mmol, 1.3 M solution in cyclohexane). After stirring for 15 min, the electrophile (MeI, Me_3SiCl or acetone) (1.0 mmol) was added all at once and the mixture stirred for additional 30 min at 175 K. After this time, 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 (3×10 mL). The combined organic phases were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (silica gel, petroleum ether/Et_2O 8:2→95:5) to afford α-functionalized epoxides **3a–c**, **8** and **9a**.

(*R*)-(−)-2-(2-Fluorophenyl)-2-methyloxirane (3a): 92%; $[\alpha]_D^{25} = -44$ (*c* = 0.8, $CHCl_3$); HPLC: Cellulose Lux 2 (250×4.6 mm), *n*-hexane/*i*PrOH 99.5:0.5, flow 0.5 mL min^{-1}, λ = 260 nm, $t_{R\,minor}$ = 12.1 min, $t_{R\,major}$ = 13.0 min; e.r. 99.5:0.5.

(±)-2-(2-Fluorophenyl)-2-trimethylsilyloxirane (3b): Colorless oil, 40%; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ = 7.31–7.28 (m, 1H; ArH), 7.22–7.19 (m, 1H; ArH), 7.11–7.08 (m, 1H; ArH), 7.01–6.98 (m, 1H; ArH), 3.02 (d, ^2J(H,H) = 5.5 Hz, 1H; CH*H*), 2.86 (d, ^2J(H,H) = 5.5 Hz, 1H; CH*H*), 0.06 (s, 9H; 3×CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ = 159.9 (d, ^1J(C,F) = 245 Hz; CF), 129.1 (d, ^3J(C,F) = 4 Hz; CH), 128.8 (d, ^2J(C,F) = 16 Hz; *C*CF), 128.2 (d, ^3J(C,F) = 7 Hz; CH), 123.9 (d, ^4J(C,F) = 2 Hz; CH), 114.9 (d, ^2J(C,F) = 21 Hz; CH), 51.4[3] (CH_2), 51.4[1] (C), −4.0 (3×CH_3); ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ = −115.78; FT-IR (film): $\tilde{\nu}$ = 3040, 2959, 1614, 1580, 1488, 1250, 842 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 210 (30) [M^+], 195 (35) [M^+−CH_3], 139 (13), 77 (100).

(±)-2-[2-(2-Fluorophenyl)oxiran-2-yl]propan-2-ol (3c): White solid, 57%, m.p. 55–56 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.45–7.43 (m, 1H; ArH), 7.32–7.29 (m, 1H; ArH), 7.14–7.12 (m, 1H; ArH), 7.06–7.02 (m, 1H; ArH), 3.41 (d, ^2J(H,H) = 5.5 Hz, 1H; CH*H*), 2.79 (d, ^2J(H,H) = 5.5 Hz, 1H; CH*H*), 2.07 (s, 1H; OH), 1.29 (d, ^6J(H,F) = 2.4 Hz, 3H; CH_3), 1.27 (s, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ = 160.3 (d, ^1J(C,F) = 247 Hz; CF), 131.0 (d, ^3J(C,F) = 3 Hz; CH), 129.8 (d, ^3J(C,F) = 8 Hz; CH), 125.3 (d, ^2J(C,F) = 14 Hz; *C*CF), 123.6 (d, ^4J(C,F) = 2 Hz; CH), 115.3 (d, ^2J(C,F) = 22 Hz; CH), 70.5 (COH), 62.7 (C), 50.6 (d, ^4J(C,F) = 1 Hz; CH_2), 26.4 (CH_3), 24.9 (d, ^5J(C,F) = 2 Hz; CH_3); ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ = −112.95; FT-IR (KBr): $\tilde{\nu}$ = 3483, 2986, 1492, 1450, 1189, 762 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 196 (1) [M^+], 138 (100), 123 (92), 109 (54), 59 (33); elemental analysis calcd (%) for $C_{11}H_{13}FO_2$: C 67.33, H 6.68; found: C 67.64, H 6.98.

Synthesis of β-aminoalcohols 4a–d and 10—General procedure: The respective and freshly distilled amine (Et_2NH, Bn_2NH, pyrrolidine or morpholine) (1.4 mmol) was added to a solution of the respective epoxide (**3a** or **9a**) (0.7 mmol in 2 mL of absolute EtOH), then the mixture was refluxed for 48 h. After this time, the solvent was evaporated in vacuo and the crude product was purified by column chromatography (silica gel, CH_2Cl_2/MeOH 97:3 → 92:8) to afford β-aminoalcohols **4a–d** and **10**.

(±)-1-(Diethylamino)-2-(2-fluorophenyl)propan-2-ol (4a): colorless oil, 95%; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ = 7.73–7.70 (m, 1H; ArH), 7.22–7.18 (m, 1H; ArH), 7.12–7.10 (m, 1H; ArH), 6.98–6.94 (m, 1H; ArH), 4.97 (br s, 1H; OH), 3.13 (dd, ^2J(H,H) = 13.5, ^5J(H,F) = 1.5 Hz, 1H; CH*H*), 2.62 (d, ^2J(H,H) = 13.5 Hz, 1H; CH*H*), 2.30–2.42 (m, 4H; 2×CH_2), 1.52 (s, 3H; CH_3), 0.88 (t, ^3J(H,H) = 7.1 Hz, 6H; 2×CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ = 159.3 (d, ^1J(C,F) = 244 Hz; CF), 135.4 (d, ^2J(C,F) = 13 Hz; *C*CF), 128.3 (d, ^3J(C,F) = 4 Hz; CH), 127.6 (d, ^3J(C,F) = 4 Hz; CH), 123.9 (d, ^4J(C,F) = 4 Hz; CH), 115.5 (d, ^2J(C,F) = 23 Hz; CH), 69.5 (d, ^3J(C,F) = 5 Hz; COH), 62.9 (d, ^4J(C,F) = 3 Hz; CH_2), 48.1 (2×CH_2), 27.6 (d, ^4J(C,F) = 4 Hz; CH_3), 11.9 (2×CH_3); ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ = −114.36; FT-IR (film): $\tilde{\nu}$ = 3368, 2972, 1385, 1482, 1448, 1204, 1062, 819, 759 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 225 (1) [M^+], 210 (6) [M^+−CH_3], 86 (100) [$C_5H_{12}N^+$], 58 (11); elemental analysis calcd (%) for $C_{13}H_{20}FNO$: C 69.30, H 8.95, N 6.22; found: C 69.65, H 9.11, N 6.30.

(±)-2-(2-Fluorophenyl)-1-(pyrrolidin-1-yl)propan-2-ol (4b): colorless oil, 95%; ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ = 7.76–7.71 (m, 1H; ArH), 7.24–7.19 (m, 1H; ArH), 7.14–7.10 (m, 1H; ArH), 6.99–6.94 (m, 1H; ArH), 3.11 (dd, ^2J(H,H) = 12.8 Hz, ^5J(H,F) = 1.5 Hz, 1H; CH*H*), 2.90 (d, ^2J(H,H) = 12.8 Hz, 1H; CH*H*), 2.43–2.27 (m, 4H; 2×CH_2), 1.65–1.60 (m, 4H; 2×CH_2), 1.52 (s, 3H; CH_3); ^{13}C NMR (125 MHz, $CDCl_3$, 298 K): δ = 159.3 (d, ^1J(C,F) = 244 Hz; C), 134.7 (d, ^2J(C,F) = 13 Hz; *C*CF), 128.4 (d, ^3J(C,F) = 8 Hz; CH), 127.8 (d, ^3J(C,F) = 4 Hz; CH), 124.1 (d, ^4J(C,F) = 2 Hz; CH), 115.5 (d, ^2J(C,F) = 24 Hz; CH), 70.6 (d, ^3J(C,F) = 5 Hz; COH), 65.2 (d, ^4J(C,F) = 4 Hz; CH_2), 55.2 (2×CH_2), 27.4[0] (CH_2), 27.3[7] (CH_2), 23.8 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ = −113.23; FT-IR (film): $\tilde{\nu}$ = 3400, 2971, 2803, 1482, 1446, 1296, 1206, 1076, 820, 759 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 223 (1) [M^+], 208 (4) [M^+−CH_3], 123 (3), 84 (100) [$C_5H_{10}N^+$], 55 (6); elemental analysis calcd (%) for $C_{13}H_{18}FNO$: C 69.93, H 8.13, N 6.27; found: C 69.80, H 8.37, N 6.27.

(±)-1-(Benzylamino)-2-(2-fluorophenyl)propan-2-ol (4c): colorless oil, 85%; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ = 7.73–7.70 (m, 1H; ArH), 7.32–7.22 (m, 6H; 6×ArH), 7.16–7.12 (m, 1H; ArH), 7.00–6.97 (m, 1H; ArH), 3.71 (s, 2H; CH_2), 3.35 (d, ^2J(H,H) = 12.0 Hz, 1H; CH*H*), 2.76 (d, ^2J(H,H) = 12.0 Hz, 1H; CH*H*), 1.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ = 159.3 (d, ^1J(C,F) = 245 Hz; CF), 139.7 (C), 133.3 (d, ^2J(C,F) = 13 Hz; *C*CF), 128.7 (d, ^4J(C,F) = 8 Hz; CH), 128.4 (2×CH), 128.2 (d, ^3J(C,F) = 5 Hz; CH), 128.0 (2×CH), 127.1 (CH), 124.0 (d, ^4J(C,F) = 2 Hz; CH), 115.7 (d, ^2J(C,F) = 24 Hz; CH), 71.6 (d, ^3J(C,F) = 5 Hz; COH), 57.7 (d, ^4J(C,F) = 4 Hz; CH_2), 53.9 (CH_2), 26.3 (d, ^4J(C,F) = 4 Hz; CH_3); ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ = −113.70; FT-IR (film): $\tilde{\nu}$ = 3338, 3063, 2931, 1579, 1484, 1451, 1210, 819, 759, 699 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 241 (3) [M^+−18], 120 (67) [$C_8H_{10}N^+$], 91 (100) [$C_7H_7^+$], 65 (7); elemental analysis calcd (%) for $C_{16}H_{18}FNO$: C 74.11, H 7.00, N 5.40; found: C 74.23, H 7.19, N 5.49.

(*R*)-(−)-(4c): 83%, $[\alpha]_D^{25} = -5.6$ (*c* = 0.9, $CHCl_3$): HPLC: Chiralcel OD-H (250×4.6 mm), *n*-hexane/*i*PrOH 95:5, flow 0.5 mL min^{-1}, λ = 230 nm, $t_{R\,minor}$ = 19.2 min, $t_{R\,major}$ = 21.1 min; e.r. 99.5:0.5.

(±)-2-(2-Fluorophenyl)-1-(morpholin-4-yl)propan-2-ol (4d): white solid, 88%, m.p. 69–70 °C (hexane); ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ = 7.71–7.68 (m, 1H; ArH), 7.24–7.14 (m, 1H; ArH), 7.13–7.10 (m, 1H; ArH), 7.00–6.95 (m, 1H; ArH), 3.85 (br s, 1H, OH), 3.57–3.54 (m, 4H; 2×CH_2), 3.14 (dd, ^2J(H,H) = 13.2, ^5J(H,F) = 1.2 Hz, 1H; CH*H*), 2.59 (d, ^2J(H,H) = 13.2 Hz, 1H; CH*H*), 2.42–2.38 (m, 2H; 2×CH*H*), 2.27–2.23

(m, 2H; 2×CH*H*), 1.52 (d, ^5J(H,F)=1.1 Hz, 3H; CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ =159.2 (d, ^1J(C,F)=244 Hz; CF), 134.6 (d, ^2J(C,F)=13 Hz; *C*CF), 128.6 (d, ^3J(C,F)=8 Hz; CH), 127.3 (d, ^3J(C,F)=4 Hz; CH), 124.2 (d, ^4J(C,F)=2 Hz; CH), 115.7 (d, ^2J(C,F)=23 Hz; CH), 70.3 (d, ^3J(C,F)=5 Hz; COH), 67.4[1] (CH_2), 67.4 (CH_2), 67.0 (CH_2), 54.8 (2×CH_2), 27.4 (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ =−113.38; FT-IR (KBr): $\tilde{\nu}$=3366, 2974, 2859, 1479, 1447, 1300, 1199, 1117, 864, 780 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 239 (3) [M^+], 208 (4), 123 (3), 84 (100) [$C_5H_{10}N^+$], 55 (6); elemental analysis calcd (%) for $C_{13}H_{18}FNO_2$: C 65.25, H 7.58, N 5.85; found: C 65.49, H 7.63, N 5.71.

(*R*)-(−)-(4d): 85%, $[\alpha]_D^{25}$=−2.0 (*c* = 0.9, $CHCl_3$); HPLC: Chiralcel OD-H (250×4.6 mm), *n*-hexane/*i*PrOH 95:5, flow 0.5 mL min^{-1}, λ=230 nm, $t_{R\,minor}$=13.3 min, $t_{R\,major}$=14.2 min; e.r. 99.5:0.5.

(±)-2-(2,4-Difluoro-3-trimethylsilylphenyl)oxirane (8): colorless oil, 90%; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ =7.16–7.12 (m, 1H; ArH), 6.80–6.77 (m, 1H; ArH), 4.08 (brs, 1H; CH), 3.15–3.14 (m, 1H; CH*H*), 2.75–2.73 (m, 1H; CH*H*), 0.38 (s, 9H; 3×CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ =166.7 (dd, ^1J(C,F)=186 Hz, ^3J(C,F)=16 Hz; CF), 165.1 (dd, ^1J(C,F)=186 Hz, ^3J(C,F)=16 Hz; CF), 128.1 (dd, ^3J(C,F)=11 Hz, ^3J(C,F)=6 Hz; CH), 120. 5 (dd, ^2J(C,F)=18 Hz, ^4J(C,F)=3 Hz; CH), 113.4 (t, ^2J(C,F)=35 Hz; CSi), 111.4 (dd, ^2J(C,F)=27 Hz, ^4J(C,F)=3 Hz; CH), 50.3 (CH), 47.0 (d, ^4J(C,F)=6 Hz; CH_2), 0.2 (3×CH_3); ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ =−98.35, −105.22; FT-IR (film): $\tilde{\nu}$=3051, 2918, 1610, 1460, 1370, 1252, 1124, 982, 846 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 228 (42) [M^+], 199 (41),136 (33), 117 (64), 77 (100).

(±)-1-(Diethylamino)-2-(3-(trifluoromethyl)phenyl)propan-2-ol (10): colorless oil, 85%; ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ =7.75 (brs, 1H; ArH), 7.62–7.61 (m, 1H; ArH), 7.47–7.46 (m, 1H; ArH), 7.43–7.41 (m, 1H; ArH), 4.72 (brs, 1H; OH), 2.84 (d, ^2J(H,H)=13.4 Hz, 1H; CH*H*), 2.66 (d, ^2J(H,H)=13.4 Hz, 1H; CH*H*), 2.41–2.28 (m, 4H; 2×CH_2), 1.47 (s, 3H; CH_3), 0.89 (t, ^3J(H,H)=7.1 Hz, 6H; 2×CH_3); ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ =150.0 (C), 130.3 (q, ^2J(C,F)=32 Hz; *C*CF_3), 128.4 (CH), 128.2 (CH), 124.3 (q, ^1J(C,F)=272 Hz, CF_3), 123.1 (CH), 121.7 (CH), 70.8 (COH), 65.2 (CH_2), 48.1 (2×CH_2), 29.5 (CH_3), 11.9 (2×CH_3); ^{19}F NMR (376 MHz, $CDCl_3$, 298 K): δ =−63.02; FT-IR (film): $\tilde{\nu}$=3338, 3063, 2931, 1579, 1484, 1451, 1210, 819, 759, 699 cm^{-1}; GC-MS (70 eV): *m*/*z* (%): 275 (3) [M^+], 120 (67), 91 (100), 65 (7); elemental analysis calcd (%) for $C_{14}H_{20}F_3NO$: C 61.08, H 7.32, N 5.09; found: C 61.29, H 7.65, N 5.40.

(*S*)-(−)-(10): 85%, $[\alpha]_D^{25}$=−2.0 (*c* = 1, $CHCl_3$); ^{1}H NMR (600 MHz, 298 K, CCl_4 with CD_3OD as external standard) in the presence of the CSA (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)ethanol, (CSA/**10** molar ratio=2:1), δ_{minor}=0.89 ppm, δ_{major}=0.86 ppm; e.r. 96:4.

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