Tetrahedron 65 (2009) 383–388

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Influence of an *ortho*-sulfinyl group on the configurational stability of α-lithiated aryloxiranes: deuteration of tolylsulfinyl styrene oxides

Vito Capriati [a], Saverio Florio [a,*], Renzo Luisi [a], Antonio Salomone [a], Maria Giovanna Tocco [a], Ana M. Martín Castro [b], José Luis García Ruano [b,*], Esther Torrente [b]

[a] *Dipartimento Farmaco-Chimico, Università di Bari, Consorzio Interuniversitario Nazionale Metodologie e Processi Innovativi di Sintesi C.I.N.M.P.I.S, Via Edoardo Orabona 4, I-70125 Bari, Italy*
[b] *Departamento de Química Orgánica (C-I), Universidad Autònoma, Cantoblanco, 28049 Madrid, Spain*

ARTICLE INFO

Article history:
Received 1 August 2008
Received in revised form
19 September 2008
Accepted 9 October 2008
Available online 14 October 2008

Keywords:
Lithiation
Phenyl sulfinyl styrene oxide
Configurational stability

ABSTRACT

The influence of the *p*-tolylsulfinyl group, located at *ortho*-, *meta*-, and *para*-position, on the regio- and stereoselectivity of the deuteration reactions of substituted styrene oxides has been investigated. The sulfinyl group at an *ortho*-position reduces the configurational stability of α-lithiated styrene oxides, whereas *meta*- and *para*-sulfinyl derivatives completely control the regioselectivity only yielding deuterated products at the aromatic ring due to its strong *ortho*-director effect.

1. Introduction

It is well-known that α-lithiated aryloxiranes (obtained by lithiation of styrene oxides) are configurationally stable intermediates,[1] whose reactions with electrophiles take place with complete retention of configuration at the benzylic carbon. However, reactions with prochiral electrophiles, such as aldehydes, afford mixtures of epimers at the hydroxylic carbon,[2] thus limiting the scope of the use of these carbanions in asymmetric synthesis. The high efficiency of the *ortho*-sulfinyl group in the stereoselectivity control of the reactions of benzylic carbanions with electrophiles is also well documented.[3] More precisely, the reactions of *ortho*-sulfinyl benzyl carbanions with prochiral electrophiles, such as imines[4] or aldehydes,[5] proceeded with high levels of stereoselectivity. This fact suggested that the presence of a sulfinyl group at the *ortho*-position of α-lithiated aryloxiranes could enhance the stereoselectivity of their reactions with prochiral electrophiles. As the first step of this research we describe herein the synthesis of optically pure 2-*p*-tolylsulfinyl styrene oxides and the results obtained in their lithiation/deuteration sequences, illustrating the influence of the sulfinyl group on the configurational stability of α-lithiated aryloxiranes.

2. Results and discussion

Diastereoisomeric 2-*p*-tolylsulfinyl styrene oxides (*S*,*Ss*)-**2a** and (*R*,*Ss*)-**3a** were prepared by the reaction of optically active (*S*)-2-*p*-tolylsulfinyl benzaldehyde **1**[6a,b] with dimethylsulfonium methylide in DMSO (Corey–Chaykovsky's epoxidation)[6c] at room temperature (10 min) (80% yield, dr **2a**/**3a**: 56/44) (Scheme 1). Although better dr values (66/34 and 71/29) were obtained when reactions were conducted in DMSO/THF at lower temperatures (0 or −40 °C, respectively) for longer reaction times (2 or 10 h), the yields were also lower (49–68%, see Section 4). Diastereoisomer **2a** could be isolated from the mixture of **2a** and **3a** in 92% de by crystallization (Et_2O/hexane). The absolute configuration of **2a** was proved to be *S*,*Ss* by desulfinylation with *n*-BuLi (50% yield) and comparison of the resulting styrene oxide with commercially available (*S*)-styrene oxide (Scheme 1).

The synthesis of optically pure (*R*,*Ss*)-2-*p*-tolylsulfinyl styrene oxide **3a** was achieved when (*R*)-2-bromostyrene oxide **4** (obtained by hydrolytic kinetic resolution[7] of racemic 2-bromostyrene oxide[8] (±)-**4** using an *R*,*R*-salen cobalt complex) was successively subjected to bromine–lithium exchange with *t*-BuLi/THF and sulfinylated with (*S*)-(−)-menthyl-*p*-toluenesulfinate (48% yield, dr 98/2) (Scheme 2).

* Corresponding authors. Tel.: +39 080 5442749; fax: +39 080 5442539 (S.F.). Tel.: +34 914974701; fax: +34 914973966 (J.L.G.R.).
E-mail addresses: florio@farmchim.uniba.it (S. Florio), joseluis.garcia.ruano@uam.es (J.L. García Ruano).

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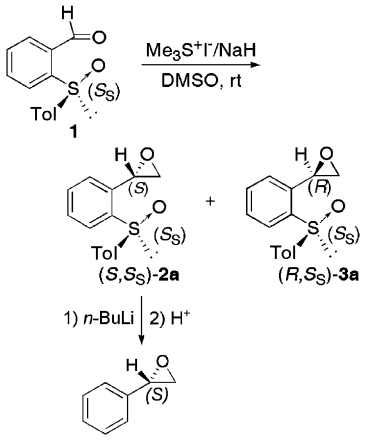
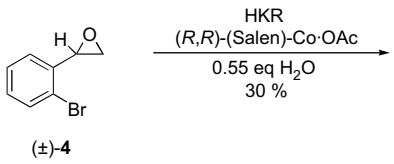
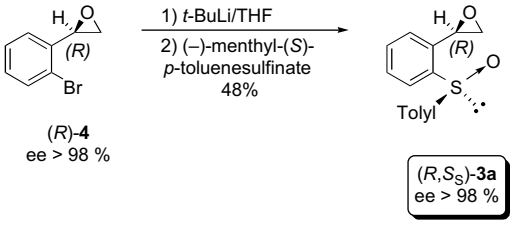
doi:10.1016/j.tet.2008.10.021



Scheme 1.





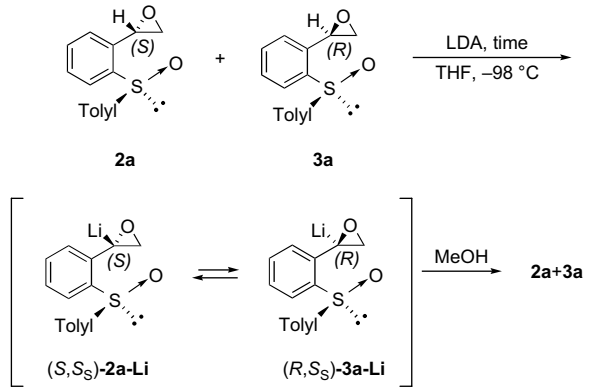
Scheme 2.

With epoxides **2a** and **3a** in hand we investigated their lithiation. A deprotonation/reprotonation sequence, run on different diastereoisomeric mixtures [dr (*S*,*Ss*)-**2a**/(*R*,*Ss*)-**3a**=37/63–86/14] with LDA/THF showed that, after acidic quenching, the final mixtures had the same composition [dr (*S*,*Ss*)-**2a**/(*R*,*Ss*)-**3a**=76/24] regardless of the composition of the starting mixture (see Table 1).

This result suggests that an epimerization probably occurs during the lithiation step. There are two possible sites where the epimerization might occur: the benzylic stereocenter of the epoxide and the sulfur atom. Both hypotheses should be demonstrated because precedent reports showed that either α-lithiated styrene oxide[2] or chiral sulfoxides[3] is configurationally stable under the reaction conditions which had been used. In order to prove that α-lithiation actually takes place with LDA, the deprotonation/deuteration sequence was investigated using several diastereoisomeric mixtures of varied composition and quenching the reaction mixture with MeOD (Table 2).

Here again, regardless of the diastereoisomeric composition of the starting mixture, almost the same final ratio [dr (*S*,*Ss*)-**2a**/(*R*,*Ss*)-**3a**=70/30–80/20] was obtained (entries 1–6, Table 2). Interestingly, by ^{1}H NMR spectroscopy it could be seen that the deuterium was incorporated at the benzylic position of the epoxide.[9] From the results collected in Table 2 some remarkable comments can be done considering the reaction time, the composition of the starting diastereoisomeric mixture, the extent of the deuteration, and the ratio of the deuterated epoxides. Starting from almost optically

Table 1
Deprotonation/reprotonation of **2a**/**3a** mixtures with LDA/MeOH

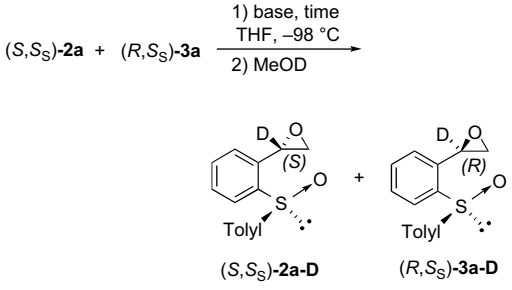


dr **2a**/**3a** before deprotonation[a,b]	Time (min)	dr **2a**/**3a** after reprotonation[a,c]
86/14	10	76/24
56/44	10	76/24
56/44	30	76/24
37/63	30	76/24

[a] Calculated by ^{1}H NMR of the crude reaction mixture.
[b] Starting value of dr for different reaction mixtures before deprotonation.
[c] Final value of dr after reprotonation.

pure (*R*,*Ss*)-**3a** (dr 96/4, er>98/2) and (*S*,*Ss*)-**2a** (dr 98/2, er>98/2), the same final ratio [dr (*S*,*Ss*)-**2a**/(*R*,*Ss*)-**3a** about 70/30] was obtained regardless of the reaction times (entries 3, 4, and 6, Table 3), thus suggesting a relatively fast deprotonation reaction. The extent of the deuteration in the final products seems to be time-dependent. However, looking at the deuterium incorporated into (*S*,*Ss*)-**2a-D** and (*R*,*Ss*)-**3a-D**, it can be seen that their ratios are opposite to those observed in the final mixtures; specifically, diastereoisomer (*R*,*Ss*)-**3a** is deuterated to a further extent than

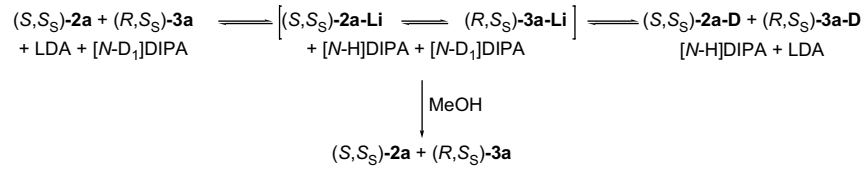
Table 2
Lithiation/deuteration sequence of mixtures of (*S*,*Ss*)-**2a** and (*R*,*Ss*)-**3a**



Entry	Base	dr **2a**/**3a** before deprotonation	*T* (min)	D%[b]	dr **2a**/**3a** after the reaction[a,c]	dr **2a-D**/**3a-D**[a]
1	LDA	65/35	15	50	70/30	39/61
2	LDA	65/35	60	21	76/24	32/68
3[b]	LDA	4/96	60	20	80/20	40/60
4	LDA	4/96	5	11	79/21	34/66
5	LDA	50/50[d]	5	30	70/30	25/75
6	LDA	98/2	15	38	70/30	33/67
7	LTMP	50/50	15	56	60/40	46/54
8	LTMP	4/96	60	50	73/27	47/53

[a] Calculated by ^{1}H NMR of the crude reaction mixture.
[b] Calculated by MS-ESI or ^{1}H NMR spectra of the crude reaction mixture.
[c] This ratio takes into consideration the contribution deriving from deuteration.
[d] 0.55 equiv of LDA were used.

Table 3
Lithiation of (*S*,*Ss*)-**2a** and (*R*,*Ss*)-**3a** in the presence of excess [*N*-D_1]DIPA



Entry	BuLi (equiv)[a]	[*N*-D_1]DIPA (equiv)[a]	dr **2a**/**3a** before deprotonation	D %[b]	dr **2a**/**3a** after the reaction[b,c]	dr **2a-D**/**3a-D**[b]
1	1.5	1.8	56/44	20	73/27	70/30
2	1.5	4.0	56/44	56	83/17	80/20

[a] Equivalents to be referred to the starting mixture of epoxides (**2a**+**3a**).
[b] Calculated by ^{1}H NMR of the crude reaction mixture.
[c] This ratio takes into consideration the contribution deriving from deuteration.

(*S*,*Ss*)-**2a**. By a HPLC analysis and by comparison with a racemic mixture of **2a** and **3a**, it was also demonstrated that the change of diastereoisomeric ratio did not affect the enantiomeric ratio of the diastereoisomers so proving that the sulfur atom did not undergo any loss of configurational integrity. Therefore, it may be concluded that the above epimerization does not involve the sulfur stereocenter; instead, it has to be ascribed to the lithiation at the benzylic center of the epoxide. This means that the latter is configurationally unstable under the conditions used and two equilibrating diastereoisomeric lithiated intermediates (*S*,*Ss*)-**2a-Li** and (*R*,*Ss*)-**3a-Li** (see Table 1) should be present in the reaction mixture. Moreover, from the deuteration experiments, it is also evident that the final ratio of (*S*,*Ss*)-**2a-D**/(*R*,*Ss*)-**3a-D** could be correlated to the ratio of the rapidly equilibrating lithiated species and the different and opposite ratio of (*S*,*Ss*)-**2a**/(*R*,*Ss*)-**3a** in the final mixtures suggests that an equilibrium between the starting epoxide and the lithiated intermediate, in the presence of LDA, may be playing a role (Eq. 1).

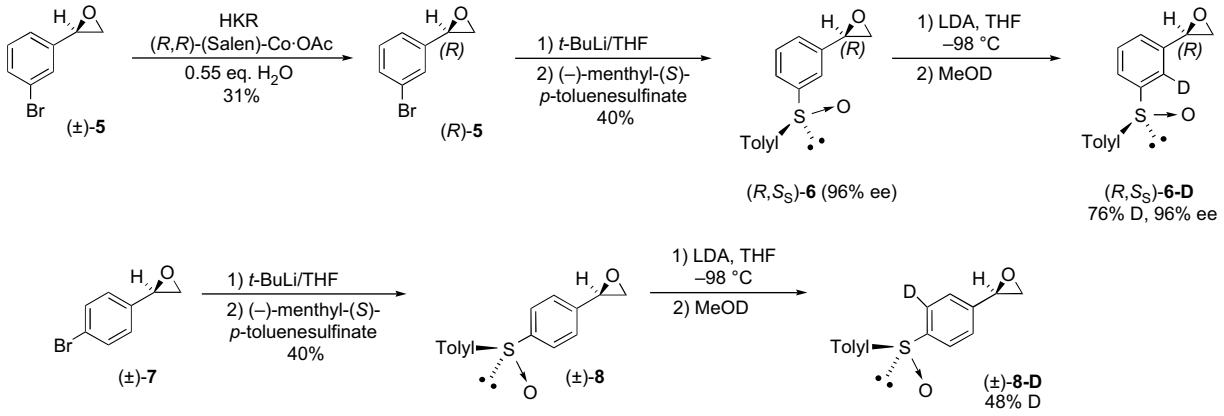
$$(S,S_S)\text{-}\mathbf{2a} + \mathrm{LDA} \rightleftharpoons \left[(S,S_S)\text{-}\mathbf{2a\text{-}Li} \rightleftharpoons (R,S_S)\text{-}\mathbf{3a\text{-}Li}\right] + \mathrm{DIPA} \rightleftharpoons (R,S_S)\text{-}\mathbf{3a} + \mathrm{LDA} \quad (1)$$

To demonstrate such an equilibrium, a mixture of (*S*,*Ss*)-**2a** and (*R*,*Ss*)-**3a** (dr=56/44) was treated in two separate experiments with 1.5 equiv of LDA, prepared from 1.5 equiv of BuLi and either 1.8 or 4.0 equiv of [*N*-D_1]diisopropylamine ([*N*-D_1]DIPA,[10] that is, with 0.3 and 2.5 excess [*N*-D_1]DIPA, respectively (entries 1 and 2, Table 3)). After quenching of the reaction mixture with MeOH, ^{1}H NMR spectroscopic analysis of the crude showed a conspicuous incorporation of deuterium (up to 56%, entry 2, Table 3) at the benzylic position of epoxides **2a** and **3a** (whose relative ratio reflected roughly those previously found, see Table 2) so supporting the hypothesis that an equilibrium between 'neutral' and lithiated diastereoisomeric epoxides may be really under way.

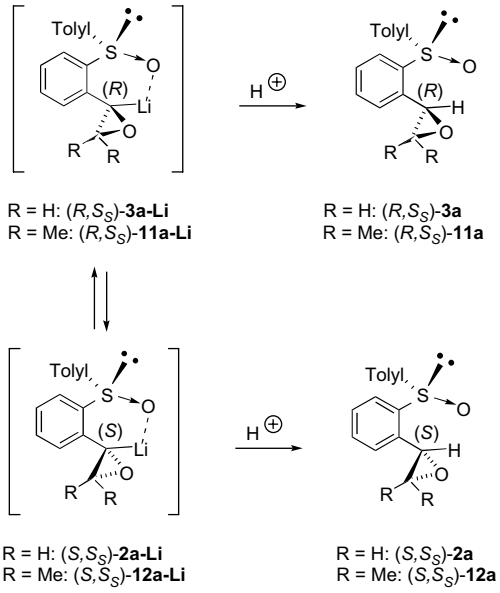
Regardless of the aggregation states and complexation phenomena, it is reasonable to assume that the pK_a of the protons to be removed in (*S*,*Ss*)-**2a** and (*R*,*Ss*)-**3a** are very close to the pK_a of DIPA (35.7 in THF)[11] and that the final ratio (*S*,*Ss*)-**2a**/(*R*,*Ss*)-**3a** and the different composition of the deuterated epoxides (*S*,*Ss*)-**2a-D**/(*R*,*Ss*)-**3a-D** may be mainly the result of a difference of the thermodynamic acidity in the protonated species. That is, under the above equilibrating conditions, should only the relative free energies of the reactants and products (which are the two diastereomeric epoxides **2a** and **3a**) be crucial in determining the position of the equilibrium. (*S*,*Ss*)-**2a** is probably slightly less acidic than (*R*,*Ss*)-**3a**, which is deprotonated faster, so giving a higher concentration of (*R*,*Ss*)-**3a-Li**, which is finally trapped as (*R*,*Ss*)-**3a-D**. Using the more basic and sterically demanding lithium tetramethylpiperidide (LTMP) (pK_a TMP=37.3 in THF)[11] comparable results were obtained (entries 7 and 8, Table 2): indeed, lithiation of different mixtures of (*S*,*Ss*)-**2a** and (*R*,*Ss*)-**3a** followed by deuteration with MeOD furnished a similar ratio for the final epoxides (*S*,*Ss*)-**2a**/(*R*,*Ss*)-**3a**, the epoxide (*S*,*Ss*)-**2a** still being the main product. On the other hand, the (*S*,*Ss*)-**2a-D**/(*R*,*Ss*)-**3a-D** ratio was slightly less shifted toward **3a-D**. It is interesting to observe that in the case of lithiation performed in the presence of an excess of [*N*-D_1]DIPA, **2a**/**3a** and **2a-D**/**3a-D** ratio are almost the same after quenching of the reaction mixture with MeOH (entries 1 and 2, Table 3). This is because, [*N*-D_1]DIPA being the only deuterium source, a hydrogen or a deuterium could be picked up with the same probability from [*N*-H]DIPA or [*N*-D_1]DIPA, respectively, by the equilibrating anions, **2a-Li** and **3a-Li**. However, as aggregation undoubtly plays a significant role on lithiation other than shifts and basicities, until the association of these lithiated epoxides will be well understood, the interpretation of the above equilibria must be made with caution.

In order to confirm the influence of the sulfinyl group on the configurational stability of the α-carbon of the styrene oxide, the role of such a group at *meta*- and *para*-position has been investigated. The needed *meta*- and *para*-sulfinyl styrene oxides were then prepared starting from 3- and 4-bromostyrenes, which were oxidized to the corresponding oxides (90% yield, *m*-CPBA, CH_2Cl_2). 3-Bromostyrene oxide (±)-**5**[7a] was subjected to hydrolytic kinetic resolution [HKR, (*R*,*R*)-(Salen)-Co·OAc] to give (*R*)-3-bromostyrene oxide (*R*)-**5** (31% yield, ee 96%), which was successively treated first with *t*-BuLi and then with (*S*)-(−)-menthyl-*p*-toluenesulfinate leading to the formation of (*R*,*Ss*)-2-[3-(*p*-tolyl)sulfinyl]styrene oxide **6** [40% overall yield, dr (*R*,*Ss*)-**6**/(*R*,*Rs*)-**6**=70/30, (*R*,*Ss*)-**6** 96% ee] (Scheme 3).[12] Epoxide **6** was first treated with LDA (1.5 equiv, THF, −98 °C) and then with MeOD to furnish epoxide **6-D** (76% D, 96% ee), deuterated only at C-2 of the phenyl ring. No α-deuteration was observed. The complete regioselectivity observed in this reaction can be explained by the *ortho*-directing effect of the sulfinyl group and the oxiranic oxygen. The lithiation/deuteration sequence of the diastereoisomeric mixture of 4-sulfinyl styrene oxide (±)-**8**, prepared from racemic 4-bromostyrene oxide (±)-**7** upon Br–Li exchange followed by sulfinylation (40%), was also studied. Lithiation (LDA, 30 min, −98 °C or −78 °C) of **8** followed by deuteration (MeOD) only produced deuterated epoxide **8-D** (48% D at −98 °C, 35% D at −78 °C) as it is indicated in Scheme 3. The complete regioselectivity observed in this reaction is not unexpected on the basis of the strong *ortho*-directing effect of the sulfinyl group.[13]

These results led us to conclude that the sulfinyl group affects the stereochemistry of the α-lithiation of styrene oxides exclusively from the *ortho*-position. The 'negative' influence of the sulfinyl group on the configurational stability of the α-lithiated aryloxiranes



Scheme 3.

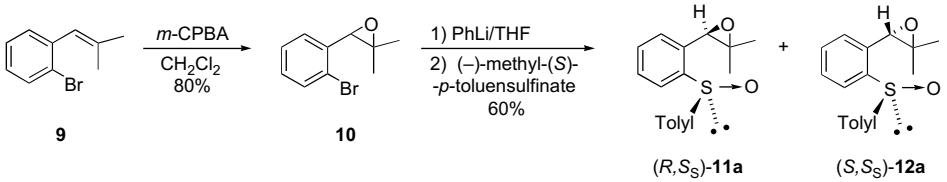


Scheme 4.

2a-Li and **3a-Li** (Scheme 4) could be explained by assuming that the coordination of the sulfinyl oxygen to the lithium would lengthen the C–Li bond in such a way to lower the inversion barrier so promoting a quick equilibration between the above lithiated species.[14] Their protonation from the less hindered face afforded **2a** and **3a**, respectively. The predominance of **2a** in the reaction mixture would suggest that its stability may be higher than that of **3a**. To verify this, preliminarily, equilibrium geometries were calculated for each diastereomer starting with a systematic conformer distribution analysis. Conformers were then grouped into families on the basis of relevant torsion angle values. The best representative of each family was submitted to a PM3 semi-empirical geometry optimization and, in order to introduce electron correlation in the computation of the energetics, we performed, on the best conformer of each analog, single-point calculations using the density functional theory (DFT) at the B3LYP/6-311+G(df,p)//PM3 level of theory.[15] Diastereoisomer (*S*,*Ss*)-**2a** resulted to be thermodynamically more stable than (*R*,*Ss*)-**3a** of 1.9 kcal/mol.

In order to improve the stereoselectivity and simultaneously support the previously indicated model, we prepared dimethyloxiranes **11a** and **12a**, following the sequence depicted in Scheme 5. The incorporation of two methyl groups at the oxirane ring might affect the relative stability of their carbanions, **11a-Li** and **12a-Li** (Scheme 4), and also that of **11a** and **12a**.

Compounds **11a** and **12a** were prepared as a 1/1 mixture by epoxidation of 2-bromophenyl 1,1-dimethylethylene[16] **9** and subsequent sulfinylation of **10** with (−)-menthyl-(*S*)-*p*-toluenesulfinate. After their chromatographic separation, configurational assignment was made by NMR spectroscopy (see Section 4). A 50/50 mixture of **11a** and **12a** was treated with LDA in THF at −98 °C for 10 min (an intense dark brown color indicates the formation of the carbanion) and then protonated with methanol at the same temperature. The resulting product is formed by an 86/14 diastereoisomeric mixture of **11a** and **12a**. When pure **11a** or **12a** were the starting materials, the composition of the reaction mixture was identical, which indicated that equilibration of the carbanions was taking place. It is noteworthy that the relative configuration of the major product **11a** is identical to that of **3a** obtained as the minor product in the reaction on the non-methylated oxirane. Similarly, experiences of deuteration provided analogous results. The deuteration degree was lower (20%) than for **2a** or **3a**. Starting from pure **11a** or **12a**, the non-deuterated compounds also appeared as an 86/14 mixture of both. Similar ab initio calculations, at the same DFT level as in the case of **2a** and **3a**, demonstrated that (*R*,*Ss*)-**11a** is, in this case, thermodynamically more stable than (*S*,*Ss*)-**12a** in about 0.8 kcal/mol.



Scheme 5.

3. Conclusion

In conclusion, we have investigated the lithiation reaction of sulfinyl-substituted styrene oxides revealing that, from the *ortho*-position, the sulfinyl group causes epimerization at the benzylic carbon of the epoxide. To the best of our knowledge, this should be the first case in which an optically active styrene oxide undergoes racemization upon lithiation, which can be rationalized by the influence of the sulfinyl group.

4. Experimental

4.1. General information

Tetrahydrofuran (THF) was freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. Petroleum ether refers to the 40–60 °C boiling fraction. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was distilled over finely powdered calcium hydride. For the ^{1}H and ^{13}C NMR spectra (^{1}H NMR 300, 400, 500 MHz; ^{13}C NMR 75, 100, 125, 150 MHz), $CDCl_3$ was used as the solvent if not specified otherwise. MS-ESI analyses were performed on LC/MSD trap system VL. Melting points were uncorrected. Optical rotation was measured with a polarimeter using a cell of 1 dm path length, the concentration (*c*) is expressed in g/100 mL. Enantiomeric purity assay was ascertained by HPLC employing a Daicel Chiralcel OD-H column (250×4.6 mm). 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 a solution of 5% (w/v) ammonium molybdate and 0.2% (w/v) cerium(III) sulfate in 100 mL 17.6% (w/v) aq sulfuric acid and heating to 200 °C for some time until blue spots appear. All reactions involving air-sensitive reagents were performed under argon in oven-dried glassware using syringe-septum cap technique.

4.2. Experimental procedures

4.2.1. Preparation of diastereoisomeric mixture of **2a** and **3a**

A solution of (*S*)-2-*p*-tolylsulfinyl benzaldehyde **1** (244 mg, 1 mmol) in 1 mL of DMSO was slowly added to a stirred solution of Me_3SI (612 mg, 3 mmol) and NaH (60% oil dispersion, 120 mg, 3 mmol, previously washed three times with hexane) in DMSO (3 mL) under Ar. After 10 min at room temperature, the resulting mixture was diluted with 6 mL of water and extracted with AcOEt (3×3 mL). The combined organic phases were washed with brine (3×3 mL) and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography (silica gel; hexane/AcOEt 1/1) to give 206 mg of sulfinyl styrene oxides **2a**+**3a** (80% yield, dr 56/44). Employing a 1/1 DMSO/THF mixture at 0 or −40 °C, a dr 66/34 (68% overall yield) or 71/29 (49% overall yield) of **2a**/**3a** was obtained, respectively. Compound **2a** was separated from a 56/44 diastereoisomeric mixture by crystallization (ether/hexane, dr **2a**/**3a**: 96/4). (*S*,*Ss*)-**2a**: 47% yield; waxy solid, $[\alpha]_D^{20}$ −105.7 (*c* 1, $CHCl_3$, 98% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.38 (dd, *J*=2.8, 5.5 Hz, 1H), 2.96 (dd, *J*=4.0, 5.5 Hz, 1H), 4.18 (dd, *J*=2.8, 4.0 Hz, 1H), 7.24 (d, *J*=8.1 Hz, 2H), 7.30 (dd, *J*=1.5, 7.7 Hz, 1H), 7.43–7.54 (m, 2H), 7.48 (d, *J*=8.1 Hz, 2H), 8.06 (dd, *J*=1.5, 7.7 Hz, 1H); ^{13}C NMR (100 MHz) δ 21.4, 48.2, 50.4, 124.2, 124.7, 125.8, 128.9, 130.0, 131.2, 135.7, 141.8, 141.9, 143.6; FTIR (KBr): 3055, 2990, 1594, 1492, 1191, 1083, 986, 877 cm^{-1}; MS (ESI): 281 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{15}H_{15}O_2S$: 259.0787. Found: 259.0790. Diastereoisomeric excess evaluated via HPLC on a Daicel Chiralcel OD-H column: *n*-hexane/*i*-PrOH 60/40, flow 0.2 mL/min [t_R(*S*,*S*-**2a**)=60.1 min, t_R(*R*,*S*-**3a**)=65.2 min].

4.2.2. Preparation of (*R*,*Ss*)-**3a**, (±)-**8**, and (*R*,*Ss*)-**6**: general procedure

A solution of (*R*)-*ortho*-, (±)-*meta*- or (*R*)-*para*-bromostyrene oxide (0.7 mmol, 140 mg) in THF (1 mL) was added to a stirred precooled solution (−78 °C, dry ice/acetone bath) of *t*-BuLi (1.4 mmol, 750 μL of a 1.7 M solution in pentane) in THF (4 mL) under Ar. After 15 min at this temperature, the resulting mixture was added via cannula to a precooled (−78 °C) solution of (*S*)-(−)-menthyl-*p*-toluenesulfinate (1 mmol, 295 mg) and TMEDA (1 mmol, 149 μL) in THF (4 mL) under Ar, stirred for an additional time of 15 min, quenched with saturated aq NH_4Cl, and extracted with AcOEt (3×5 mL). The solvent was removed under reduced pressure and the crude residue purified by flash chromatography (silica gel; hexane/AcOEt 1/1). (*R*,*Ss*)-**3a**: 50% yield, colorless oil, dr 98/2, $[\alpha]_D^{20}$ −189.6 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.60 (dd, *J*=2.9, 5.9 Hz, 1H), 3.04 (dd, *J*=3.9, 5.9 Hz, 1H), 4.23 (dd, *J*=2.9, 3.9 Hz, 1H), 7.26 (d, *J*=7.9 Hz, 2H), 7.33 (d, *J*=6.9 Hz, 1H), 7.44–7.48 (m, 2H), 7.50 (d, *J*=7.9 Hz, 2H), 7.89 (d, *J*=6.9 Hz, 1H); ^{13}C NMR (125 MHz) δ 21.3, 48.8, 51.8, 125.3, 125.4, 128.9, 130.0, 131.6, 136.2, 141.1, 141.6, 143.6; FTIR (neat): 3055, 2990, 1594, 1492, 1191, 1083, 986, 877 cm^{-1}; MS (ESI): 281 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{15}H_{15}O_2S$: 259.0787. Found: 259.0792. (±)-**8**: 40% yield, oil, inseparable mixture of diastereoisomers, dr 50/50; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 2.69 (2×dd, *J*=2.6, 4.4 Hz, 1H), 3.10 (d, *J*=2.6, 4.4 Hz, 1H), 3.83 (dd, *J*=2.6, 4.0 Hz, 1H), 7.22 (d, *J*=8.4 Hz, 2H), 7.32 (d, *J*=8.4 Hz, 2H), 7.49 (d, *J*=8.4 Hz, 2H), 7.58 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz) δ 21.3, 51.3, 51.6, 124.72, 124.74, 124.76, 124.8, 126.2, 129.9, 140.81, 140.82, 141.61, 141.64, 142.2, 145.5; FTIR (neat): 3051, 2922, 1492, 1087, 1046, 877, 834, 810 cm^{-1}; MS (ESI): 281 $[M+Na]^+$. (*R*,*Ss*)-**6** and (*R*,*Rs*)-**6**: 40% overall yield, colorless oil, inseparable mixture of diastereoisomers by column chromatography, dr 70/30 in favor of (*R*,*Ss*)-**6** (evaluated by ^{13}C NMR), 96% ee (HPLC, Daicel Chiralcel OD-H column: *n*-hexane/*i*-PrOH 90/10, flow 1.0 mL/min [t_R(*R*,*Ss*)=21.0 min, t_R(*S*,*Ss*)=25.0 min); ^{1}H NMR (400 MHz, $CDCl_3$) (major) δ 2.37 (s, 3H), 2.75 (dd, *J*=2.2, 5.5 Hz, 1H), 3.14 (dd, *J*=4.0, 5.5 Hz, 1H), 3.87 (dd, *J*=2.2, 4.0 Hz, 1H), 7.26 (d, *J*=8.1 Hz, 2H), 7.32 (d, *J*=7.3 Hz, 1H), 7.42 (t, *J*=7.7 Hz, 1H), 7.52–7.54 (m, 3H), 7.59 (s, 1H); ^{13}C NMR (150 MHz) δ 21.2, 51.2, 51.7, 121.4, 124.2, 124.8, 127.6, 129.2, 129.9, 139.3, 141.6, 142.1, 146.2; FTIR (neat): 3052, 2922, 1597, 1493, 1476, 1088, 1047, 884, 811 cm^{-1}; MS (ESI): 281 $[M+Na]^+$.

4.2.3. Preparation of (±)-**10**: general procedure

To a solution of 2-bromophenyl 1,1-dimethylethylene **9**[13] (1.0 mmol, 210 mg) in 10 mL of anhydrous dichloromethane, cooled at 0 °C, was slowly added 70% *m*-CPBA (1.5 mmol, 365 mg) and the reaction mixture was stirred overnight at room temperature. Then, it was quenched with satd $NaHSO_3$ (10 mL). The organic layer was washed with satd $NaHCO_3$ (10 mL) and the aqueous layers were extracted with CH_2Cl_2 (3×15 mL). Collected organic layers were dried over Na_2SO_4 and evaporated in vacuo. The residue was purified by flash chromatography (silica gel, hexane/AcOEt 6/1). (±)-**10**: 86% yield, colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.54 (s, 3H), 3.86 (s, 1H), 7.17–7.12 (m, 1H), 7.31–7.28 (m, 2H), 7.52 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (75 MHz) δ 18.2, 24.2, 61.1, 65.0, 122.1, 127.1, 128.4, 128.8, 131.8, 136.7. MS (ESI): 227 $[M+H]^+$; HRMS (ESI) Calcd for $C_{10}H_{12}OBr$: 227.0055. Found: 227.0066.

4.2.4. Preparation of (*R*,*Ss*)-**11a** and (*S*,*Ss*)-**12a**: general procedure

To a precooled solution (−78 °C, dry ice/acetone bath) of *ortho*-bromo 2,2-dimethylstyrene oxide **10** (1 mmol, 322 mg) in THF (6 mL) was added a solution of PhLi (1.56 mmol, 870 μL of a solution 1.8 M in cyclohexane/ether). After 30 min at this temperature, the resulting mixture was added via cannula to a precooled solution (−78 °C) of (*S*)-(−)-menthyl-*p*-toluenesulfinate (1 mmol, 295 mg) in 4 mL of THF under Ar, stirred for an additional time of 15 min,

quenched with saturated solution aq NH_4Cl, and extracted with CH_2Cl_2. The solvent was removed under reduced pressure and the crude residue was purified by flash chromatography (silica gel, hexane/AcOEt 4/1). (*R*,*Ss*)-**11a**: 30% yield, colorless oil, $[\alpha]_D^{20}$ −71.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.53 (s, 3H), 1.26 (s, 3H), 2.37 (m, 3H), 3.94 (s, 1H), 7.26–7.22 (m, 2H), 7.36–7.32 (m, 1H), 7.57–7.43 (m, 4H), 8.12 (m, 1H); ^{13}C NMR (75 MHz) δ 17.2, 21.4, 24.1, 61.6, 62.1, 124.1, 127.0, 127.1, 128.7, 129.9, 130.5, 134.3, 141.5, 142.2, 142.5. FTIR (KBr): 3055, 2923, 1594, 1495, 1492, 1178, 1089, 916 cm^{-1} MS (ESI): 287 $[M+H]^+$; HRMS (ESI) Calcd for $C_{17}H_{19}O_2S$: 287.1092. Found: 287.1100. (*S*,*Ss*)-**12a**: 30% yield, colorless oil, $[\alpha]_D^{20}$ −23.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.90 (s, 3H), 1.43 (s, 3H), 2.37 (m, 3H), 3.84 (s, 1H), 7.28–7.22 (m, 2H), 7.55–7.42 (m, 4H), 7.67–7.64 (m, 1H), 7.94–7.91 (m, 1H); ^{13}C NMR (75 MHz) δ 18.2, 21.3, 24.0, 61.2, 61.4, 124.8, 125.7, 127.5, 129.1, 129.9, 130.7, 135.2, 141.5, 142.3; FTIR (KBr): 3055, 2940, 1594, 1493, 1178, 1083, 916, 877 cm^{-1}. HRMS (ESI) Calcd for $C_{17}H_{19}O_2S$: 287.1092. Found: 287.1102.

The absolute configuration of the stereogenic center of oxiranes **11a** and **12a** was assigned by comparison with the chemical shift (^{1}H NMR and ^{13}C NMR) of **2a** and **3a** on the signal corresponding to the benzylic position (C–H).

*4.2.5. Lithiation/deuteration reaction of **2a**, **3a**, **6**, (±)-**8**, **11a**, and **12a**: general procedure*

A solution of sulfinyl styrene oxides **2a**, **3a**, **6**, **8**, **11a**, or **12a** (0.2 mmol) in THF (1 mL) was added to a stirred solution of 0.3 mmol of LDA (generated by reaction of 1.8 equiv of DIPA and 1.5 equiv of *n*-BuLi 2.5 M in hexanes) in THF (3 mL) at −98 °C (liquid nitrogen/methanol bath) under Ar. After 10–60 min at this temperature, the resulting mixture was quenched with 200 μL of CH_3OD, diluted with brine, and extracted with AcOEt (3×5 mL). The solvent was removed under reduced pressure and the crude residue purified by flash chromatography (silica gel, hexane/AcOEt 1/1). (*R*)-**5**: $[\alpha]_D^{20}$ −8.3 (*c* 1, $CHCl_3$, 96% ee), lit. 7a; (*S*)-**5**: $[\alpha]_D^{20}$ +4.0 (*c* 1.1, $CHCl_3$, 35% ee,); (±)-**5** separated on a Daicel Chiralcel column: *n*-hexane/*i*-PrOH 99.5/0.5, flow 1.0 mL/min, t_R[(*R*)-**5**]=9.9 min, t_R[(*S*)-**5**]=10.6 min. (*R*)-**4**: $[\alpha]_D^{20}$ −62.5 (*c* 1, $CHCl_3$, 96% ee), lit. 6a; (*S*)-**4**: $[\alpha]_D^{20}$ +68.7 (*c* 1.1, $CHCl_3$, 99% ee,); (±)-**4** separated on a Daicel Chiralcel column: *n*-hexane/*i*-PrOH 99.5/0.5, flow 1.0 mL/min, t_R[(*R*)-**4**]=6.8 min, t_R[(*S*)-**4**]=7.2 min.

Acknowledgements

This work was carried out under the framework of the National Project 'Stereoselezione in Sintesi Organica: Metodologie ed Applicazioni' supported by the MIUR (Rome), by the University of Bari, and by the Interuniversities Consortium CINMPIS.

We thank DGITYC (Grant CTQ2006-06741/BQU) for financial support. One of us (E.T.) thanks Ministerio de Educación y Ciencia (Spain) for a predoctoral fellowship, and the Universidad Autónoma de Madrid for financial support of a predoctoral stay.

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