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Stereoselective synthesis of 2,3-epoxy alcohols mediated by a remote sulfinyl group

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ABSTRACT

The influence of the sulfinyl group as a chiral auxiliary in the stereoselective addition of oxiranyllithiums to (*S*)-2-*p*-tolylsulfinylbenzaldehyde has been studied. All reactions evolve with retention of configuration at the starting lithiated carbon. Completely stereoselective additions have been observed when configurations at sulfur and the lithiated carbon are different (matched pair), whereas variable dr's values (ranging between 52:48 and >99:<1%) when they are identical (mismatched pair).

1. Introduction

Chiral α,β-epoxy alcohols are versatile and useful building blocks for asymmetric organic synthesis since they exhibit three adjacent potentially stereogenic functionalized carbons liable to be further elaborated.[1] The oxiranyl anion-based methodology has been reported as a valuable method for preparing functionalized epoxides.[2] α-Lithiated styrene oxides have been reported to be chemically and configurationally stable, and their reaction with a series of electrophiles evolve stereospecifically into differently substituted epoxides.[3] Similarly, lithium oxazolinyloxiranes have also been trapped with electrophiles to provide functionalized oxiranes.[4] However, despite the wide scope of this methodology, the reactions of the above lithium oxiranes with aldehydes evolved with poor diastereoselectivities,[3c,4c] and mixtures of epimers at the newly generated carbinolic carbon were obtained. Recent reports have demonstrated that the sulfinyl group in *ortho* position of benzaldehydes is able to control the stereoselective addition of some nucleophiles to the carbonyl group[5] mainly when reactions take place in the presence of some Lewis acids, such as $Yb(OTf)_3$ or $Y(OTf)_3$. Bearing in mind these facts we reasoned that the reactions of lithium oxiranes with optically pure 2-*p*-tolylsulfinylbenzaldehydes could evolve in a highly stereoselective manner as a result of a double asymmetric induction process. Moreover the discrimination exerted by the sulfinyl group on the diastereotopic faces of the carbonyl could be, in principle, increased by coordination of the sulfinyl oxygen with the lithium at the oxirane, which would determine an intramolecular and consequently more stereoselective nucleophilic attack.

In the present paper we report the results obtained in the reactions of (*S*)-2-*p*-tolylsulfinylbenzaldehyde (**1**) with the differently substituted oxiranyllithiums derived from oxiranes bearing an oxazoline subunit **2**–**4** shown in Figure 1 and the influence of the different relative configurations of substrate and reagents on the stereoselectivity of the process. In addition to the methodologic interest of the study, the resulting 2,3-epoxy alcohols can be considered as potential starting materials for the synthesis of chiral α-substituted α,β-dihydroxy β-phenylpropionic acids by nucleophilic opening of the three-membered ring.[6]

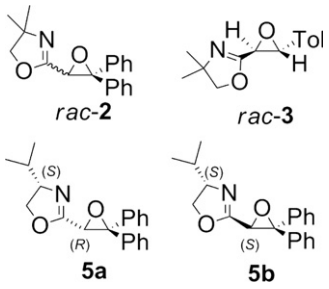

Figure 1.

2. Result and discussion

Enantiomerically pure (*S*)-2-*p*-tolylsulfinylbenzaldehyde (**1**) was synthesized in high overall yield (91%)[7] by sulfinylation of the

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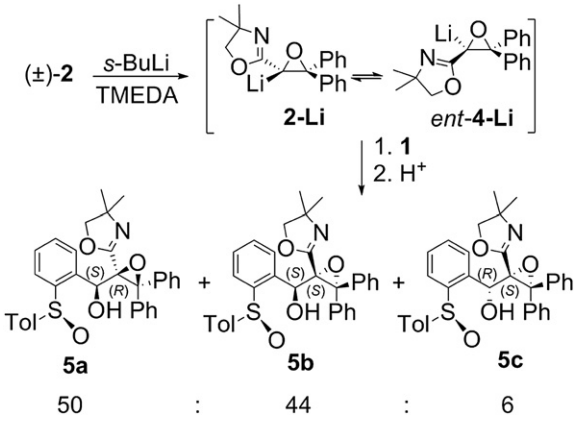
commercially available 2-bromobenzaldehyde diethyl acetal and subsequent hydrolysis of the acetal function.

Oxazolinyl diphenyl and *p*-tolyloxiranes **2** and **3** (Fig. 1) were prepared by reaction of lithiated 2-chloromethyl-4,4-dimethyloxazoline with the suitable substituted carbonyl compound, as reported.[4a–c] Chiral (*S*)-4-isopropyloxazolinyloxirane **4** was prepared as a 45:55 diastereoisomeric mixture at C-1 (**4a** and **4b**) (Fig. 1) in 60% overall yield, by lithiation of (*S*)-2-chloromethyl-4-isopropyloxazoline with LDA, followed by lithium–titanium transmetalation with Ti(*i*-PrO)$_4$ and subsequent addition of diphenylketone, as reported.[8] As the lithium derivative of **4** is most likely configurationally unstable,[9] the diastereoisomeric mixture **4a**+**4b** was used for further reactions without a preliminary separation.

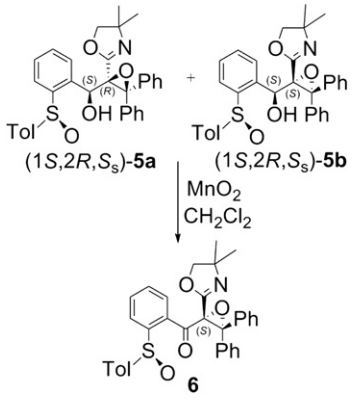
Initially, we studied the reaction of racemic 2-oxazolinyl-3,3-diphenyloxirane (**2**) with (*S*)-2-*p*-tolylsulfinylbenzaldehyde (**1**). Compound **2** was rapidly lithiated when treated with *s*-BuLi/TMEDA in THF at −98 °C, affording presumably interchangeable enantiomeric anions **2**-**Li** and *ent*-**2**-**Li**,[10] which reacted with **1** to give a 50:44:6 mixture of diastereoisomeric sulfinyl hydroxybenzyl oxazolinylepoxides **5a**–**c** (Scheme 1), in 65% combined yield. These isomers could be separated by column chromatography and crystallization.



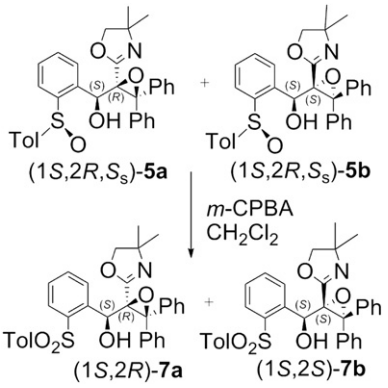
Scheme 1.

When the reaction was performed under Yb(OTf)$_3$ catalysis, the obtained yield decreased (presumably due to the attack of the acid on the epoxide) but the stereoselectivity remained almost unaltered. Similar stereochemical results were observed when the reaction was conducted in the presence of 12-crown-4 ether, able to trap the Li^+ cation. These results could suggest that the role played by both the Lewis acid and the Li^+ cation in the observed stereoselectivity must be scarcely significant.[11] Absolute configuration of (1*S*,2*S*,S_S)-**5b** was unequivocally determined by X-ray diffraction studies of its crystals.[12] Chemical correlation of **5c** with **5b** (MnO_2 oxidation of their mixture provides ketone **6** only, Scheme 3) allowed us to assign 1*R*,2*S*,S_S configuration to **5c**. This unequivocal assignment indicates that **5b** and **5c** derive from *ent*-**2**-**Li**, whose reaction with **1** is highly but not completely stereoselective (88:12 dr), since the configuration at oxiranic carbon of the resulting epoxy alcohols must be coincident with the configuration at the precursor lithium anion.

In turn, the results depicted in Scheme 2 suggest that **5a** should derive from **2**-**Li**. The oxidation of **5a** and **5b** with *m*-CPBA afforded two diastereoisomeric sulfones **7a** and **7b**. As their configuration at the oxiranyl carbon must be the opposite (**5a** and **5b** derive from **2**-**Li** and *ent*-**2**-**Li**, respectively), we can conclude that the configuration at the carbinolic carbon is the same (*S*) for both **7a** and **7b**, and, therefore, for **5a** and **5b** (Scheme 3).



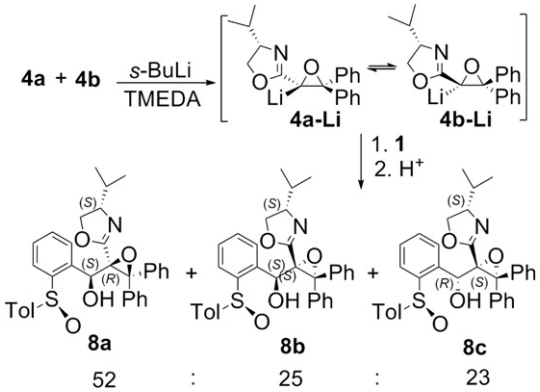
Scheme 2.



Scheme 3.

From these studies a significant role of the sulfinyl group can be inferred in the control of the configuration at the carbinolic carbon, determining a completely stereoselective evolution of **2**-**Li**, yielding **5a** only, and a highly stereoselective transformation of *ent*-**2**-**Li** to give a 88:12 mixture of **5b** and **5c**.

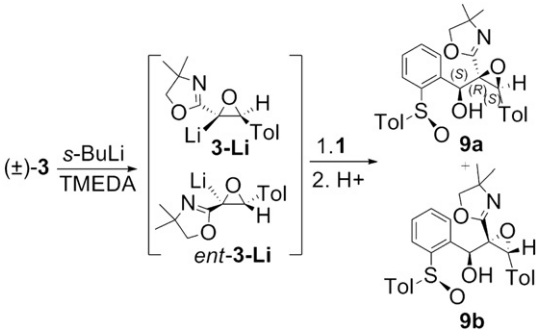
Then, we studied the influence of an additional stereogenic centre at the skeleton of nucleophile on the stereoselectivity of the process. To this purpose, oxazolines **4a** and **4b** were synthesized (see above) and used as an epimeric mixture at C-1 because of the presumed configurational instability of the corresponding lithiated derivatives **4a**-**Li** and **4b**-**Li** (Scheme 5).[9] Reaction of a 55:45 mixture of **4a**+**4b** with (*S*)-2-*p*-tolylsulfinylbenzaldehyde (**1**) also afforded a 52:25:23 mixture of three epoxy alcohols **8a**–**c**, in 45% combined yield (Scheme 4).



Scheme 4.

If the reactivity of **4a**-**Li** and **4b**-**Li** is assumed to be similar, these results suggest a completely stereoselective evolution of **4a**-**Li** [as it was also the case for **2**-**Li** (Scheme 2)], which is scarcely affected by the additional chiral centre at the oxazoline. However, the diastereoselectivity of **4b**-**Li** was quite low, in contrast with that of *ent*-**2**-**Li** (Scheme 2), which indicates the negative influence of the additional chiral centre in this transformation. These results could be interpreted in terms of matched pair (**1**/**2a**) and mismatched pair (**1**/**4b**).

Next, we investigated the nucleophilic addition of the anion derived from *trans*-1-(4,4-dimethyl-2-oxazolinyl)2-*p*-tolylepoxyethane (**3**) to aldehyde **1**. Despite having used racemic (±)-**3** as the substrate (in order to obtain the stereochemical information about both enantiomers simultaneously), this reaction can be performed independently from any of them, because their synthesis had been previously reported.[4a] Oxiranyllithiums formed by deprotonation of **3** with *s*-BuLi/TMEDA (Scheme 5) have been reported to be configurationally stable for at least 1 h at −100 °C,[4b,c] in contrast to those generated from the *cis* ones. As we started from (±)-**3**, a 1:1 mixture of enantiomeric anions **3**-**Li** and *ent*-**3**-**Li** was formed, both acting as nucleophiles towards (*S*)-2-*p*-tolylsulfinylbenzaldehyde (**1**). The formation of a 1:1 mixture of diastereomeric epoxy alcohols **9a** (24% isolated yield) and **9b** (26% isolated yield) suggests that the reactions of **3**-**Li** and *ent*-**3**-**Li** with aldehyde **1** are both completely stereoselective (Scheme 5).[13]



Scheme 5.

Assuming that enantiomeric oxiranyllithiums **3**-**Li** and *ent*-**3**-**Li** are configurationally stable, the favoured attacked diastereotopic carbonyl face of **1** being the same as that observed in the reactions of **2**-**Li** and *ent*-**2**-**Li** (Scheme 1), the absolute configurations of **9a** and **9b** should be those depicted in Scheme 5 (i.e., identical configuration at both carbinolic carbon and sulfur but different at the oxiranyl centres). These assignments were confirmed by the NMR parameters of their hydroxylic protons. Compounds **9a** and **9b** exhibit similar chemical shifts (4.06 ppm for **9a** and 4.18 ppm for **9b**), but very different vicinal coupling constants, 11.0 Hz for **9a** and smaller than 1.0 Hz for **9b** (the latter indeed appearing as a broad singlet). Their δ values suggest that the hydroxylic hydrogen in both compounds is involved in intramolecular hydrogen bonding. Its association to the oxiranyl oxygen, as reported for similar *syn*-epoxy alcohols,[4b] determines that benzylic and hydroxylic protons adopt a rigid *anti* conformation (Fig. 2), thus justifying a large value of the vicinal coupling constant. This *syn* stereochemistry has been assigned to isomer **9a** showing a J_{H-OH}=11.0 Hz. In turn, for the *anti* isomer **9b** (where a similar intramolecular association is not possible for steric reasons) another hydrogen bonding can be now postulated but with the sulfinyl oxygen, so leaving both hydroxylic and benzylic protons in a *quasi gauche* arrangement; this accounts for the observed small vicinal coupling constant value (Fig. 2).

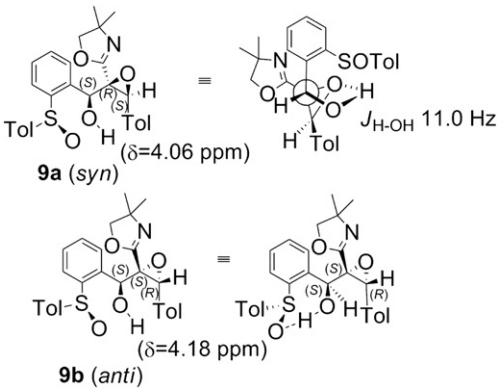


Figure 2.

As a summary of the stereochemical results obtained in this paper, we can conclude that the reactions of the studied oxiranyllithiums with 2-*p*-tolylsulfinylbenzaldehyde (**1**) evolve with complete retention of the configuration at the lithiated carbon, as it happened with all the reactions with carbonyl compounds, which had been previously reported,[4] evidencing a scarce or no influence of the sulfinyl group at that reaction site. By contrast, the chiral auxiliary exerts a significant role on the stereochemical control at the hydroxylic centre. Compounds **9a** and **9b**, both with the *S* configuration at carbinolic carbon (Scheme 5), are exclusively formed in the reactions with oxiranyllithiums **3**-**Li** (with *R* configuration at the nucleophilic carbon) and *ent*-**3**-**Li** (with *S* configuration at the nucleophilic carbon). The high stereoselectivity can be explained taking into account what it should be the preferred conformation of compound **1** (depicted in Fig. 3) in terms of electrostatic interactions (indeed, the negatively charged carbonyl oxygen atom interacts with the positively charged sulfinyl sulfur atom). The tolyl group hinders the approach of the oxiranyllithium from the upper face of the carbonyl group, thus privileging adducts with *S* configuration at the carbinolic carbon.

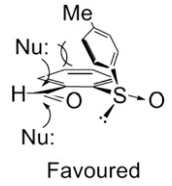


Figure 3. Favoured approach of nucleophile to the most stable conformation aldehyde **1**.

This complete control of the stereoselectivity was observed in all the reactions with oxiranyllithiums exhibiting *R* configuration at the nucleophilic carbon (**4a**-**Li** and **2**-**Li**), according to the matched pair protocol (*R*-configured nucleophilic carbon and *S*-sulfur at electrophile). By contrast, the stereoselectivity control was partially lost in the reactions involving the enantiomeric oxiranyllithiums **4b**-**Li** and *ent*-**2**-**Li**, both *S*-configured at the nucleophilic carbon, which conform the mismatched pair (*S* anionic carbon and *S* sulfur atom). Nevertheless, alcohols with the *S* configuration at the carbinolic carbon were always the major products. In the case of **4b**-**Li** and *ent*-**2**-**Li** the presence of a phenyl group at C-3 position of the oxirane ring in *cis* arrangement with respect to the oxazoline ring, might cause changes in the spatial arrangement of both groups provoking steric interactions disfavouring the approach of the lithiated species to the most stable conformation of aldehyde **1**. This effect, which should be much more severe for **4b**-**Li** with a bulky *i*-Pr group at the oxazoline ring, would shift the conformational equilibrium of **1** towards other conformations, which would evolve

into (*R*)-alcohols, with the consequent detriment of the stereoselectivity. However, the accurate structure of the operative transition state cannot be easily conceived.

3. Conclusions

In conclusion, the previously observed low stereoselectivity observed in reactions of oxiranyllithiums with carbonyl compounds[3c,4c] has been efficiently circumvented by incorporation onto the reactive nucleophile of a chiral sulfinyl group having the suitable configuration at sulfur (the opposite one to that of the oxiranyllithium).

4. Experimental

4.1. General information

NMR spectra were obtained in a Bruker spectrometer (300 and 75 MHz for ^{1}H and ^{13}C NMR, respectively) in $CDCl_3$ solutions. Melting points were measured using a *Gallemkamp* apparatus in open capillary tubes. Mass spectra (MS) were determined by ESI, using an HP1100MSD apparatus. Specific optical rotations were measured in a *Perkin–Elmer* 241 MC polarimeter. All reactions were carried out in anhydrous solvents under argon atmosphere. Commercially available anhydrous tetrahydrofuran (THF) was dried over 4 Å molecular sieves. Flash column chromatography was performed using silica gel Merck-60 (230–400 mesh).

4.2. Experimental procedures

Oxyranes *rac*-**2**, *rac*-**3** and **4a**,**4b** and (*S*)-2-*p*-Tolylsulfinylbenzaldehyde (**1**) were synthesized following the experimental protocol described in the bibliography.

4.2.1. General procedure for the synthesis of 2,3-epoxy alcohols. To a precooled solution (−98 °C, methanol/liq N_2) of the corresponding oxyrane (**2**, **3**, **4a** or **4b**) (1.0 mmol) and TMEDA (3.0 mmol) in THF (7.0 mL) under argon, was added a solution of *s*-BuLi (1.4 mmol, 0.86 mL, 1.4 M in hexane). After 15 min, a solution of (*S*)-2-*p*-tolylsulfinylbenzaldehyde **1** (1.0 mmol, 268 mg) in THF (1.0 mL) was slowly added. The resulting mixture was stirred at −98 °C for 30 min, then is quenched with a saturate solution of NH_4Cl (2.0 mL) and extracted with AcOEt (3×20.0 mL). Collected organic layers were dried over anhydrous Na_2SO_4 and evaporated in vacuo. The residue was purified by flash column chromatography employing Et_2O–AcOEt 7:3 as the eluent.

*4.2.1.1. [1S,2R,S$_S$], [1S,2S,S$_S$] and [1R,2S,S$_S$]-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3,3-diphenyloxiran-2-yl]-[2-(p-tolylsulfinyl)phenyl]methanol (**5a**+**5b**+**5c**).* The diastereoisomer mixture **5a**:**5b**:**5c** (50:44:6) was obtained using oxyrane *rac*-**2** as the nucleophile. The diastereoisomeric were separated and purified by flash column chromatography (eluent Et_2O–AcOEt 7:3). Combined yield (for diastereoisomeric mixture): 65%. Diastereoisomer [1*S*,2*R*,*S*$_S$]-**5a**: yield: 33%, white solid; $[\alpha]_D^{20}$ −148.1 (*c* 1.0, $CHCl_3$); mp: 196–197 °C; IR (film): 3391, 2968, 2932, 1659, 1443, 1078, 1024, 754, 702 cm^{-1}; ^{1}H NMR: *δ* 8.05 (dd, *J* 7.8 and 1.3 Hz, 1H), 7.59–7.24 (m, 15H), 7.00 (d, *J* 8.1 Hz, 2H), 5.86 (d *J* 11.0 Hz, 1H), 4.22 (d, *J* 10.9 Hz, 1H), 3.61 (d, *J* 8.1 Hz, 1H), 3.17 (d, *J* 8.1 Hz, 1H), 2.30 (s, 3H), 1.05 (s, 3H), 0.89 (s, 3H) ppm; ^{13}C NMR: *δ* 161.9, 145.8, 141.9, 140.5, 138.8, 137.7, 136.5, 130.0, 129.5, 128.8, 128.4, 128.2, 128.0, 127.0, 126.8, 126.1, 125.8, 125.2, 78.8, 71.5, 71.4, 67.9, 66.2, 27.6, 27.5, 21.4 ppm; MS (ESI$^+$) *m*/*z* 538 [M+H]$^+$; HRMS (ESI$^+$): calcd for $C_{33}H_{32}NO_4S$: 538.2052; found: 538.2065. Diastereoisomer [1*S*,2*S*,*S*$_S$]-**5b**: ^{1}H NMR (83:17 mixture of **5b**+**5b**): *δ* 8.15 (dd, *J* 7.9 and 1.2 Hz, 1H), 7.84–7.82 (m, 2H), 7.65–7.28 (m, 13H), 7.08 (d, *J* 8.1 Hz, 2H), 6.15 (d *J* 10.0 Hz, 1H), 4.72 (d, *J* 9.6 Hz, 1H), 3.66 (d, *J* 8.2 Hz, 1H), 3.18 (d, *J* 8.2 Hz, 1H), 2.32 (s, 3H), 1.11 (s, 3H), 1.05 (s, 3H) ppm; ^{13}C NMR: *δ* 162.1, 144.7, 142.9, 141.1, 138.2, 136.6, 130.4, 129.7, 129.2, 128.8, 128.5, 128.0, 127.6, 126.7, 126.3, 125.9, 124.5, 78.6, 72.5, 69.4, 68.0, 65.9, 27.8, 27.7, 21.3 ppm. Diastereoisomer [1*R*,2*S*,*S*$_S$]-**5c** was obtained by crystallization of the diastereoisomeric mixture **5b**+**5c** (CH_2Cl_2–hexane): yield: 28%, white solid; $[\alpha]_D^{20}$ −76.5 (*c* 1.0, $CHCl_3$); mp: 116–118 °C; IR (film): 3320, 3057, 2981, 2928, 1678, 1494, 1100, 1032, 729 cm^{-1}; ^{1}H NMR: *δ* 7.76 (dd, *J* 7.9 and 1.1 Hz, 1H), 7.59 (d, *J* 8.3 Hz, 2H), 7.54–7.51 (m, 4H), 7.36–7.12 (m, 11H), 7.0 (d *J* 8.1 Hz, 1H), 5.41 (s, 1H), 3.60 (br s, 1H), 3.52 (d, *J* 8.1 Hz, 1H), 3.49 (d, *J* 8.1 Hz, 1H), 2.35 (s, 3H), 0.96 (s, 3H), 0.63 (s, 3H) ppm; ^{13}C NMR: *δ* 160.4, 145.5, 142.6, 140.5, 137.9, 136.6, 130.3, 129.6, 129.2, 128.6, 128.4, 128.3, 127.9 (2C), 127.1, 127.0, 125.9, 125.7, 79.3, 71.5, 71.3, 68.1, 67.1, 27.5 (2C), 21.4 ppm; MS (ESI$^+$) *m*/*z* 538 [M+H]$^+$; HRMS (ESI$^+$): calcd for $C_{33}H_{32}NO_4S$: 538.2052; found: 538.2057.

*4.2.1.2. [1S,2R,S$_s$], [1S,2S,S$_s$] and [1R,2S,S$_s$]-[2-(4S)-Isopropyl-4,5-dihydrooxazol-2-yl-3,3-diphenyloxiran-2-yl]-[2-(p-tolylsulfinyl)phenyl]methanol (**8a**+**8b**+**8c**).* The diastereoisomeric mixture **8a**:**8b**:**8c** (52:25:23) was obtained when using a 55:45 mixture of **4a**+**4b** as the nucleophile. The diastereoisomers mixture were separated and purified by flash column chromatography (eluent Et_2O–AcOEt 7:3). Combined yield (for diastereoisomer mixture): 45%. Diastereoisomer [1*S*,2*R*,*S*$_s$]-**8a**: yield: 27%, white solid; $[\alpha]_D^{20}$ −72.0 (*c* 1.0, $CHCl_3$); mp: 185–187 °C; IR (film): 3235, 3059, 2962, 2923, 1667, 1456, 1023, 750 cm^{-1}; ^{1}H NMR: *δ* 7.70 (dd, *J* 7.9 and 1.0 Hz, 1H), 7.50 (d, *J* 8.3 Hz, 2H), 7.44–7.35 (m, 4H), 7.28–7.10 (m, 10H), 6.90 (d *J* 7.4 Hz, 1H), 5.17 (br s, 1H), 3.93 (br s, 1H), 3.84 (dd, *J* 8.1 and 9.6 Hz, 1H), 3.74–3.66 (m, 1H), 3.52 (dd, *J* 7.9 and 7.7 Hz, 1H), 2.27 (s, 3H), 1.23–1.10 (m, 1H), 0.55 (d, *J* 6.8 Hz, 3H), 0.44 (d, *J* 6.8 Hz, 3H) ppm; ^{13}C NMR: *δ* 162.3, 145.6, 142.4, 140.5, 138.0, 136.8, 136.6, 130.1, 129.5, 129.0, 128.3, 128.1, 128.0, 127.9, 127.7, 127.0, 126.0, 125.8, 125.7, 72.8, 71.9, 71.8, 70.7, 68.4, 32.0, 21.3, 18.5, 17.9 ppm; MS (ESI$^+$) *m*/*z* 552 [M+H]$^+$; HRMS (ESI$^+$): calcd for $C_{34}H_{34}NO_4S$: 552.2130; found: 552.2132. Diastereoisomer [1*S*,2*S*,*S*$_s$]-**8b** and [1*R*,2*S*,*S*$_s$]-**8c**: yellow solid; IR (film): 3301, 3061, 2973, 2965, 1701, 1652, 1455, 1030, 912, 734 cm^{-1}; ^{1}H NMR (56:44 mixture of **8b**+**8b**): *δ* 8.10–8.04 (m, 2H), 7.93–7.87 (m, 2H), 7.68–7.23 (m, 3H), 7.61–7.17 (m, 25H), 7.08 (d, *J* 8.3 Hz, 2H), 7.01 (d, *J* 8.1 Hz, 2H), 6.34 (d, *J* 10.3 Hz, 2H), 6.21 (d, *J* 11.1 Hz, 1H), 4.70 (d, *J* 10.3 Hz, 1H), 4.22 (d, *J* 11.1 Hz, 1H), 3.98 (dd, *J* 9.7 and 8.5 Hz, 1H), 3.76–3.62 (m, 3H), 3.53–3.41 (m, 1H), 3.16 (dd, *J* 9.6 and 8.7 Hz, 1H), 2.32 (s, 3H), 2.29 (s, 3H), 1.45 (m, 1H), 1.26 (m, 1H), 0.86 (d, *J* 6.8 Hz, 3H), 0.68 (d, *J* 6.5 Hz, 3H), 0.65 (d, *J* 6.8 Hz, 3H), 0.61 (d, *J* 6.8 Hz, 3H) ppm; ^{13}C NMR (56:44 mixture of **8b**+**8c**): *δ* 164.2, 163.5, 145.7, 145.4, 141.9, 141.6, 140.8, 140.5, 138.8, 138.7, 137.8, 137.5, 134.9, 134.2, 130.7, 130.3, 130.2, 129.7, 129.6, 129.5, 129.1, 128.8, 128.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.3, 127.1, 126.7, 126.6, 126.5, 126.0, 125.9, 125.4, 125.1, 72.4, 72.3, 72.1, 71.8, 71.7, 71.7, 70.3, 70.1, 69.9, 66.5, 65.7, 32.4, 32.3, 21.3, 21.2, 18.9, 18.6, 18.5, 18.4 ppm; MS (ESI$^+$) *m*/*z* 552 [M+H]$^+$; HRMS (ESI$^+$): calcd for $C_{34}H_{34}NO_4S$: 552.2130; found: 552.2136.

*4.2.1.3. [1S,2R,3S,S$_s$] and [1S,2R,3R,S$_s$]-[2-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-3-p-tolyl-oxiranyl]-[2-(p-tolylsulfinyl)phenyl]methanol (**9a**+**9b**).* The diastereoisomeric mixture **9a**:**9b** (50:50) was obtained using oxirane *rac*-**3** as the nucleophile. The diastereoisomers were separated and purified by flash column chromatography (eluent Et_2O–AcOEt 7:3). Diastereoisomer [1*S*,2*R*,3*S*,*S*$_s$]-**9a**: yield: 24%, white solid; $[\alpha]_D^{20}$ −128.6 (*c* 0.5, $CHCl_3$); pf: 160–158 °C; IR(film): 3328, 3055, 2970, 2926, 1655, 1457, 1187, 1033, 812 cm^{-1}; ^{1}H NMR: *δ* 8.07 (dd, *J* 7.9 and 1.3 Hz, 1H), 7.53–7.35 (m, 5H), 7.21 (d, *J* 8.1 Hz, 2H), 7.13 (d, *J* 8.1 Hz, 2H), 6.99 (d, *J* 8.1 Hz, 2H), 5.47 (br s, 1H), 4.44 (s, 1H), 4.18 (br s, 1H), 4.01 (d, *J* 8.1 Hz, 1H), 3.94 (d, *J* 8.1 Hz, 1H), 2.41 (s, 3H), 2.31 (s, 3H), 1.32 (s, 3H), 1.09 (s, 3H) ppm; ^{13}C NMR: *δ* 162.2, 145.8, 141.7, 140.5, 138.7, 138.2, 129.8, 129.4, 129.1, 128.6, 126.5, 126.3, 126.1, 125.2, 79.1, 69.5, 68.3, 62.4,

60.4, 28.0, 27.9, 21.3 (2C) ppm; MS (ESI^+) *m*/*z* 476 $[M+H]^+$; HRMS (ESI^+): calcd for $C_{28}H_{30}NO_4S$: 476.1895; found: 476.1894. Diastereoisomer [1*S*,2*R*,3*R*,S_s]-**9b**: yield: 26%, white solid; $[\alpha]_D^{20}$ −135.5 (*c* 1.0, $CHCl_3$); mp: 157–155 °C; IR (film): 3324, 3053, 2971, 2928, 1656, 1457, 1187, 1031, 812, 732 cm^{-1}; ^1H NMR: δ 8.08 (dd, *J* 7.9 and 1.1 Hz, 1H), 7.42–7.37 (m, 1H), 7.29–7.19 (m, 3H), 7.06 (d, *J* 8.1 Hz, 2H), 6.70–6.89 (m, 5H), 5.33 (d, *J* 11.0 Hz, 1H), 4.76 (s, 1H), 4.06 (d, *J* 11.0 Hz, 1H), 4.01 (d, *J* 8.1 Hz, 1H), 3.91 (d, *J* 8.1 Hz, 1H), 2.38 (s, 3H), 2.26 (s, 3H), 1.26 (s, 3H), 1.03 (s, 3H) ppm; ^{13}C NMR: δ 161.3, 145.3, 141.4, 140.8, 137.8, 137.7, 129.5, 129.2, 129.1, 128.8, 128.3, 126.6, 126.1 125.8 125.2, 78.9, 70.9, 68.0, 61.8, 60.7, 27.8, 27.6, 21.5, 21.1 ppm; MS (ESI^+) *m*/*z* 476 $[M+H]^+$; HRMS (ESI^+): calcd for $C_{28}H_{30}NO_4S$: 476.1895; found: 476.1894.

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10. The occurrence of an equilibrium between the two enantiomeric lithiated species seems reasonable also considering that, to date, α-lithiated β,β-disubstituted oxazolinyloxiranes always proved to be configurationally unstable on both microscopic and macroscopic time scales. See Ref. 9b,c.
11. However, the role of lithium in the course of the reaction cannot be definitively ruled out bearing in mind that previous spectroscopic studies demonstrated that lithium in 2-lithio-3,3-dimethyl-2-oxazolinyloxirane is either strongly intramolecularly coordinated within the same aggregate or involved in tying two monomeric units to give oxazoline-bridged dimers (see Ref. 9c).
12. Crytallographic data for the structural analysis have been deposited at the Cambrigde Crystallographic data Centre, CCDC No. 749559 for the compound **5b**. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambrigde, CB2 1FZ. UK.
13. A possible alternative kinetic resolution, with only one of the anions (**3**-**Li** or *ent*-**3**-**Li**) reacting with **1** in a very low stereoselective way, was readily ruled out since the recovered unreacted oxirane **4** resulted to be racemic as determined by chiral stationary phase HPLC.