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# Lithiation of optically active oxazolinyloxiranes: configurational stability

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**Abstract**—The α-lithiation reaction of optically active oxazolinyloxiranes has been investigated. The trapping reaction with $D_2O$, MeI and acetone affording substituted oxazolinyloxiranes proved that the corresponding lithiated species are configurationally unstable. A stereoconvergency was observed in the case of lithiation–deuteration sequence of two oxazolinyloxiranes.


## 1. Introduction

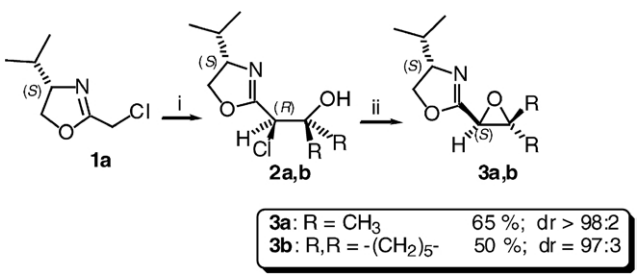
The synthesis of functionalized oxiranes using oxiranyl anion methodology is a useful and convenient synthetic procedure.[1] Numerous biologically important molecules containing the oxirane moiety in their skeleton have been prepared by such a methodology.[2] One major point in stereoselective syntheses based on this methodology is the configurational stability of the oxiranyl anions (as well as chemical stability). With stabilized oxiranyl anions the configurational stability is usually dependent upon the nature of the stabilizing group.[2d,3] Silyl, arylsulfonyl, dialkoxyphosphinyl, ethoxycarbonyl, cyano, trifluoromethyl, benzothiazolyl, oxazolinyl and unsaturated organyl groups (aryl, vinyl and alkynyl) proved to be the most efficient oxiranyl anion stabilizing groups. All these groups facilitate the oxiranyl anion formation by promoting deprotonation and prolonging its solution lifetime so that capture with electrophiles is made possible.

In previous papers[4] we reported that oxazolinyloxiranes can be easily deprotonated either α or β with respect to the oxazoline ring and the resulting oxazolinyloxiranyllithiums can be trapped with electrophiles. α-Lithiated oxazolinyloxiranes proved to be chemically and configurationally stable so that, under appropriate conditions, the trapping of the *cis* and *trans* lithiated derivatives with electrophiles took place with retention of configuration. A sort of stereoconvergency was observed with lithiated chiral oxazolinyloxiranes.

α-Lithiated oxazolinyloxiranes showed a configurational stability that allowed the preparation of useful intermediates in organic synthesis such as α,β-epoxy-γ-butyrolactones, and in highly enantioenriched form when an optically active oxazolinyloxirane was used as the precursor.[4b] In this paper we report on the reaction of α-lithiated oxiranes, prepared from chiral non-racemic oxazolinyloxiranes, with electrophiles, particular attention being addressed to the involved stereochemistry.

## 2. Result and discussion

Our work started with the preparation of the required oxazolinyloxiranes.[5] Lithiation of (4*S*)-2-chloromethyl-4-isopropyl-2-oxazoline **1a**, carried out with lithium diisopropylamide (LDA) in THF at −98°C, followed by lithium–titanium transmetalation performed with Ti(*i*-PrO)$_4$, and acetone addition, provided at first the chlorohydrin **2a** (not isolated), and later epoxide (1*S*,4′*S*)-**3a** upon treatment with NaOH in *i*-PrOH in a very high diastereoselectivity (dr >98:2). The same procedure using cyclohexanone as the carbonyl compound allowed the preparation of epoxide (2*S*,4′*S*)-**3b** (dr = 97:3) (Scheme 1).[6]




**Scheme 1.** Preparation of enantioenriched oxazolinyloxiranes **3a**,**b**. *Conditions:* (i) (a) LDA/Ti(*i*-PrO)$_4$, THF, −98°C, 10 min. (b) $R_2C{=}O$. (ii) NaOH/*i*-PrOH.

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Lithiation of (1*S*,4′*S*)-**3a**, performed with *s*-BuLi/TMEDA in THF at −98°C, and trapping with $D_2O$, afforded a 1:1 diastereomeric mixture of deuterated (1*S*,4′*S*)-**3a**-**D** and (1*R*,4′*S*)-**4a**-**D**, as ascertained by $^1H$ NMR and GLC analysis (Scheme 2).

In a similar way, the lithiation–deuteration sequence carried out on oxazolinyloxirane (2*S*,4′*S*)-**3b**, at different reaction times, led to a diastereomeric mixture of oxazolinyloxiranes (2*S*,4′*S*)-**3b**-**D** and (2*R*,4′*S*)-**4b**-**D**.

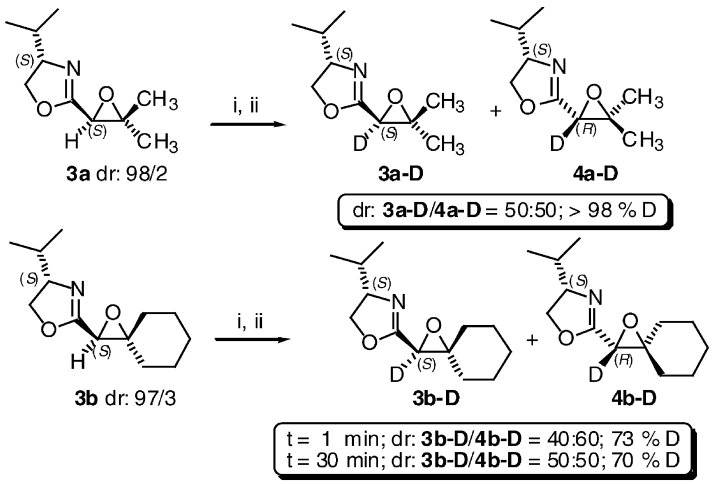
The reaction of lithiated (2*S*,4′*S*)-**3b** with different electrophiles such as MeI and acetone gave a 1:1 diastereomeric mixture of oxazolinyloxiranes (2*S*,4′*S*)-**6a**, (2*R*,4′*S*)-**6b** and (2*S*,4′*S*)-**7a**, (2*R*,4′*S*)-**7b**, respectively (Scheme 3).

These results are a clear indication that lithiated species **3a**,**b**-**Li** are configurationally unstable and tend to interconvert. Such a diastereomeric interconversion could be accounted for with the intermediacy of the lithium azaenolates **5a**,**b**-**Li** as previously proposed for other optically active oxazolinyloxiranyllithiums (Scheme 4).[4a]

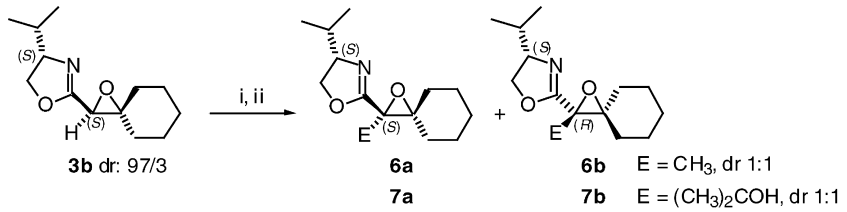
On this basis, the final functionalized epoxides **3a**,**b**-**D**, **4a**,**b**-**D**, **6a**,**b** and **7a**,**b** should form from the related lithiated precursors **3a**,**b**-**Li** and **4a**,**b**-**Li**, respectively.

The steric or coordinating effect of the substituent on the above diastereomeric interconversion was investigated. To this end we synthesized the epoxide (2*S*,4′*S*,5′*S*)-**3c** with a reasonable diastereoselectivity (dr 85:15), starting from (4*S*,5*S*)-2-chloromethyl-4-methoxymethyl-4-phenyl-2-oxazoline **1b** according to the reported procedure.[5] Deprotonation of (2*S*,4′*S*,5′*S*)-**3c** (*s*-BuLi/TMEDA, THF, −98°C) followed by deuteration ($D_2O$) gave a 1:1 diastereomeric mixture of deuterated (2*S*,4′*S*,5′*S*)-**3c**-**D** and (2*R*,4′*S*,5′*S*)-**4c**-**D**, thus proving the configurational instability of the lithiated intermediate **3c**-**Li**.[7] Therefore, there is evidence for the absence of steric and coordinating effects of substituents on the C-4 and C-5 of the oxazoline ring, probably as they are too far away from the reaction centre. Therefore, we may reasonably say that the lithiation of oxazolinyloxiranes of the type **3a**–**c** leads to lithiated species **3a**–**c**-**Li** which are configurationally unstable and tend to epimerize to **4a**–**c**-**Li** with the consequence that the trapping with electrophiles actually takes place with no diastereoselectivity.

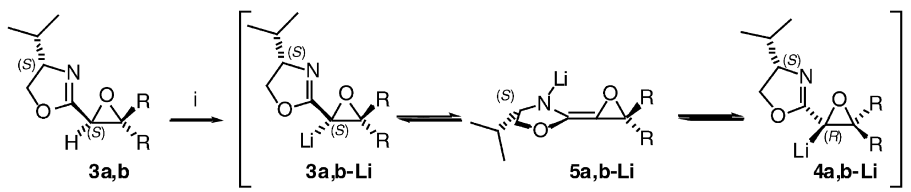
A step forward of our investigation was the study of the deprotonation-trapping sequence of optically active oxazolinyloxiranes having two stereocenters on the oxirane ring.[5b] (4*S*)-2-chloromethyl-4-isopropyl-2-oxazoline **1a** was first lithiated with LDA, then transmetalated with



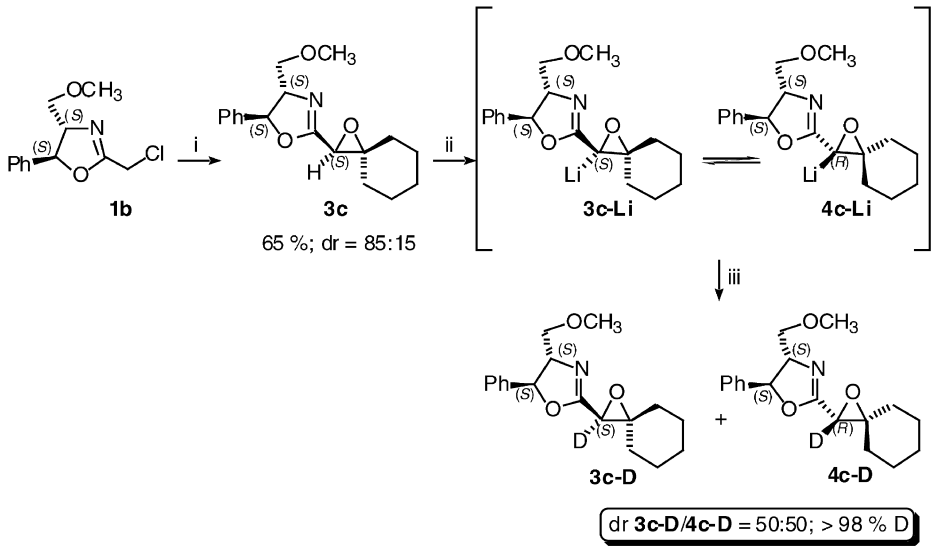

**Scheme 2.** Deprotonation of oxazolinyloxiranes **3a**,**b**. *Conditions:* (i) *s*-BuLi/TMEDA, THF, −98°C. (ii) $D_2O$.




**Scheme 3.** *Conditions:* (i) *s*-BuLi/TMEDA, THF, −98°C. (ii) Electrophile (MeI, acetone).



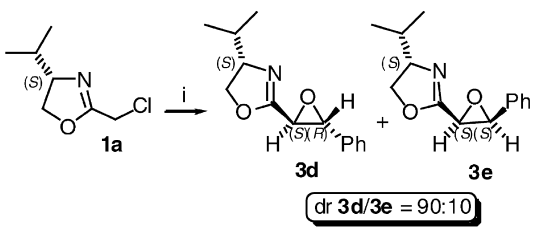

**Scheme 4.** *Conditions:* (i) *s*-BuLi/TMEDA, THF, −98°C.




**Scheme 5.** Preparation and deuteration of oxazolinyloxirane **3c**. *Conditions:* (i) (a) LDA/Ti(*i*-PrO)$_4$, THF, −98°C, 10 min. (b) Cyclohexanone. (c) NaOH/*i*-PrOH. (ii) *s*-BuLi/TMEDA, THF, −98°C, 30 min. (iii) $D_2O$.

Ti(*i*-PrO)$_4$, reacted with PhCHO and finally treated with NaOH to give a mixture (dr *trans*/*cis* 90:10) of epoxides (4*S*,2′*S*,3′*R*) *trans*-**3d** (er >98:2, $[\alpha]_D$=+65) and (4*S*,2′*S*,3′*S*) *cis*-**3e** (er >98:2, $[\alpha]_D$=−79), which were separated by column chromatography (Scheme 6). The absolute configuration of *trans*-epoxide **3d** was secured by an X-ray analysis.[4b]

*trans*-Epoxide **3d** was first lithiated (*s*-BuLi/TMEDA, THF or $Et_2O$) and then deuterated with $D_2O$ to give a completely deuterated diastereomeric mixture (dr *trans*/*cis*=90:10) of

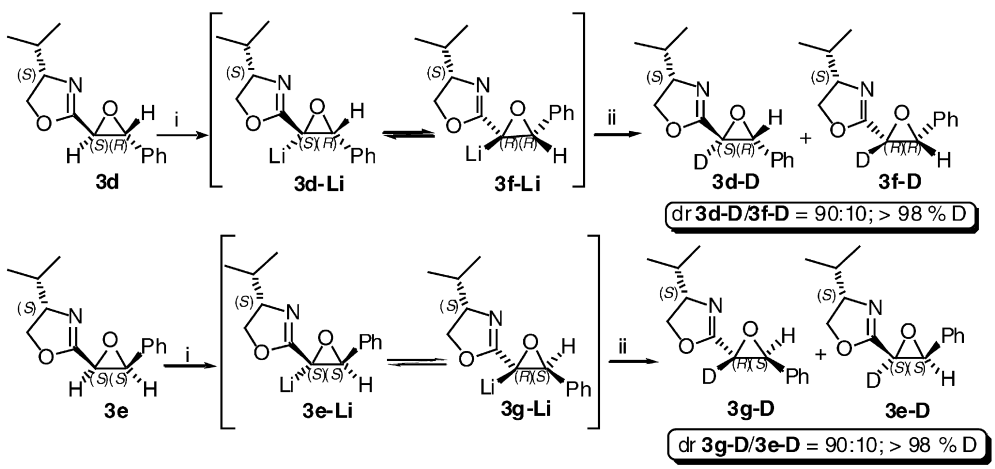



**Scheme 6.** Preparation of oxazolinyloxiranes **3d**,**e**. *Conditions:* (i) a) LDA/Ti(*i*-PrO)$_4$, THF, −98°C, 10 min. (b) PhCHO. (c) NaOH/*i*-PrOH.

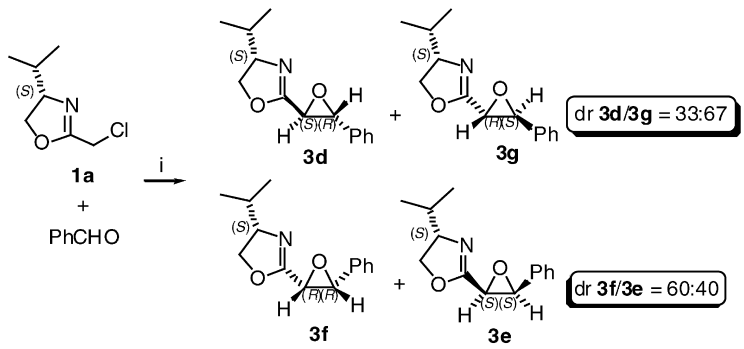
epoxides (4*S*,2′*S*,3′*R*) *trans*-**3d-D** and (4*S*,2′*R*,3′*R*) *cis*-**3f-D** (Scheme 7). It is worth pointing out that epoxide *trans*-**3d-D** showed the same $[\alpha]_D$=+66 as its precursor *trans*-**3d** ($[\alpha]_D$=+65). These results might be rationalized with the existence of a dynamic equilibrium between the lithiated species **3d-Li** and **3f-Li**, the former being the more stable of the two. Accordingly, the lithiation–deuteration sequence of (4*S*,2′*S*,3′*S*) *cis*-epoxide **3e** afforded deuterated diastereomers (4*S*,2′*R*,3′*S*) *trans*-**3g-D** ($[\alpha]_D$=−152) and (4*S*,2′*S*,3′*S*) *cis*-**3e-D** (dr *trans*/*cis*=90:10) (Scheme 7).

These data seem to suggest that lithiated species **3e-Li** and **3f-Li**, both of *cis* configuration, tend to equilibrate with the *trans*-counterparts **3g-Li** and **3d-Li** with the latter being favored over the former for steric reasons. The consequence is that the *trans* deuterated epoxides form prevalently, independently of the configuration of the starting epoxide.

In order to also unambiguously assign the configuration to the epoxides *cis*-**3f-D**, and *trans*-**3g-D** we prepared all four possible diastereomers that can derive from (4*S*)-2-chloromethyl-4-isopropyl-2-oxazoline **1a** and PhCHO. To this




**Scheme 7.** *Conditions:* (i) *s*-BuLi/TMEDA, THF (or $Et_2O$), −98°C, 30 min. (ii) $D_2O$.




**Scheme 8.** *Conditions:* (i) (a) LDA, THF, −98°C, 30 min. (b) $H^+$.

end, **1a** was lithiated with LDA and then treated with benzaldehyde.[8] We obtained a mixture of all the four possible diastereomers **3d**–**g** that could be separated by preparative HPLC and spectroscopically characterized. Their data matched quite well those of the above deuterated epoxides **3d**–**g**-**D** (Scheme 8).[9]

## 3. Conclusion

In conclusion, lithiation of optically active oxazolinyloxiranes **3a**–**e** produces oxazolinyloxiranyllithiums which are chemically stable, at least at low temperature, but configurationally unstable and exist as equilibrating diastereomers. Subsequent trapping with electrophiles proceeds with practically no diastereoselectivity. Deuteration, methylation and hydroxyalkylation in all cases studied yielded diastereomeric mixtures. A type of stereoconvergency was observed in the lithiation–deuteration of the optically active *cis* and *trans* oxazolinyloxiranes **3d** and **3e**, the explanation residing in the higher stability of the resulting lithiated species **3d**-**Li** and **3g**-**Li** with respect to **3f**-**Li** and **3e**-**Li**, respectively. The effect of the electrophile on the diastereoselectivity has also been studied later and is reported in the accompanying paper which follows.[10]

## 4. Experimental

### 4.1. General

Tetrahydrofuran (THF) and diethyl ether ($Et_2O$) were freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was distilled over finely powdered calcium hydride. Oxazolinyloxiranes **3a**–**e** were prepared following a reported procedure.[5] All other chemicals were of commercial grade and used without further purification. Petroleum ether refers to the 40–60°C boiling fraction. Commercial solutions of *n*-BuLi (2.5 M solution in hexanes) and *s*-BuLi (1.3 M solution in cyclohexane) were titrated by using *N*-pivaloyl-*o*-toluidine prior to use.[11] For $^1H$ and $^{13}C$ NMR ($^1H$ NMR 300, 500 MHz; $^{13}C$ NMR 75.4, 125 MHz), $CDCl_3$ was used as solvent. GC-MS spectrometry analyses were performed on a gas chromatograph HP 6890 plus (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a 5973 mass selective detector operating at 70 eV (EI). MS-ESI analyses were performed on Agilent 1100 LC/MSD trap system VL. Prep. HPLC separations were performed on Waters Prep 4000 with PDA UV detector. Melting points were uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished by UV light (254 nm) or by exposing to $I_2$ vapours. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

**4.1.1. (1*S*,4′*S*)-(−)-2-Methyl-1-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1,2-epoxypropane (3a).** Oil (55%), $[\alpha]_D^{20}=-79$ (*c* 1, $CHCl_3$), $^1H$ NMR (500 MHz) $\delta$: 0.85 (d, *J*=6.7 Hz, 3H), 0.92 (d, *J*=6.7 Hz, 3H), 1.36 (s, 3H), 1.38 (s, 3H), 1.74 (octet, *J*=6.7 Hz, 1H), 3.41 (s, 1H), 3.96–3.98 (m, 2H), 4.23–4.28 (m, 1H). $^{13}C$ NMR (125 MHz) $\delta$: 17.9, 18.6, 24.1, 32.2, 57.1, 60.1, 70.1, 72.2, 162.8. GC-MS *m*/*z* (rel. int.): 183 ($M^+$, 3), 142 (21), 114 (29), 84 (100), 116 (50), 91 (45), 68 (61), 45 (52). FT-IR (film) $cm^{-1}$: 2961, 1671 (C=N), 1380, 1252, 975.

**4.1.2. (2*S*,4′*S*)-(−)-4-Isopropyl-2-(1-oxaspiro[2.5]oct-2-yl)-4,5-dihydrooxazole (3b).** Oil (48%), $[\alpha]_D^{20}=-35$ (*c* 1, $CHCl_3$), dr 97:3, $^1H$ NMR (500 MHz) $\delta$: 0.81 (d, *J*=6.8 Hz, 3H), 0.87 (d, *J*=6.8 Hz, 3H), 1.35–1.75 (m, 11H), 3.36 (s, 1H), 3.85–4.05 (m, 2H), 4.17–4.25 (m, 1H). $^{13}C$ NMR (125 MHz) $\delta$: 17.8, 18.4, 24.6, 24.8, 25.2, 28.9, 32.1, 36.6, 57.0, 64.6, 69.9, 72.0, 162.7 (C=N). GC-MS *m*/*z* (rel. int.): 223 ($M^+$, 8), 180 (30), 142 (32), 124 (71), 81 (100), 41 (29). FT-IR (film) $cm^{-1}$: 2933, 2859, 1674 (C=N), 1447, 979.

**4.1.3. (4*S*,2′*S*,3′*S*)-(−)-4-Isopropyl-2-(3-phenyloxiranyl)-4,5-dihydrooxazole (3e).** Oil (5%), $\alpha_D=-79$ (*c* 0.95, $CHCl_3$), $^1H$ NMR (500 MHz) $\delta$: 0.61 (d, *J*=6.6 Hz, 3H), 0.67 (d, *J*=6.6 Hz, 3H), 1.51 (octet, *J*=6.6 Hz, 1H), 3.60 (t, *J*=8.4 Hz, 1H), 3.75–3.85 (m, 1H), 3.90 (d, *J*=4.2 Hz, 1H), 4.04 (dd, *J*=9.7, 8.4 Hz, 1H), 4.22 (d, *J*=4.2 Hz, 1H), 7.20–7.40 (m, 5H). $^{13}C$ NMR (125 MHz) $\delta$: 17.6, 18.2, 31.8, 53.2, 57.5, 69.8, 71.9, 126.5, 127.8, 128.1, 133.4, 161.1. GC-MS *m*/*z* (rel. int.): 231 ($M^+$, 11), 202 (19), 162 (15), 134 (100), 106 (19), 91 (22), 77 (15).

**4.1.4. (4*S*,2′*R*,3′*R*)-(−)-4-Isopropyl-2-(3-phenyloxiranyl)-4,5-dihydrooxazole (3f).** Oil (7%), $\alpha_D^{20}=-63$ (*c* 0.9, $CHCl_3$), $^1H$ NMR (500 MHz) $\delta$: 0.61 (d, *J*=6.7 Hz, 3H), 0.72 (d, *J*=6.7 Hz, 3H), 1.35 (octet, *J*=6.7 Hz, 1H), 3.65–3.78 (m, 2H), 3.86 (d, *J*=4.2 Hz, 1H), 3.97–4.05 (m, 1H), 4.24 (d, *J*=4.3 Hz, 1H), 7.20–7.50 (m, 5H). $^{13}C$ NMR (125 MHz) $\delta$: 18.1, 18.5, 32.4, 53, 57.7, 70.4, 72.4, 126.8, 128.1, 133.1, 160.7. GC-MS *m*/*z* (rel. int.): 231 ($M^+$, 11), 202 (19), 162 (15), 134 (100), 106 (19), 91 (22), 77 (15).

**4.1.5. (4*S*,2′*R*,3′*S*)-(−)-4-Isopropyl-2-(3-phenyloxiranyl)-4,5-dihydrooxazole (3g).** Oil (10%), $\alpha_D$=−152 (*c* 1, $CHCl_3$), $^1$H NMR (500 MHz) $\delta$: 0.91 (d, *J*=6.7 Hz, 3H), 1.05 (d, *J*=6.7 Hz, 3H), 1.77 (octet, *J*=6.7 Hz, 1H), 3.68 (d, *J*=1.9 Hz, 1H), 3.93–3.98 (m, 1H), 4.02 (t, *J*=8.3 Hz, 1H), 4.17 (d, *J*=1.9 Hz, 1H), 4.35 (dd, *J*=9.6, 8.3 Hz, 1H), 7.20–7.40 (m, 5H). $^{13}$C NMR (125 MHz) $\delta$: 18.2, 18.8, 32.5, 54.7, 57.8, 70.7, 72.6, 125.7, 128.5, 128.7, 135.3, 162.4. GC-MS *m*/*z* (rel. int): 231 ($M^+$, 11), 202 (19), 162 (15), 134 (100), 106 (19), 91 (22), 77 (15).

### 4.2. General procedure for the lithiation of oxazolinyloxiranes 3a–e and reaction with electrophiles

A solution of the oxazolinyloxirane (0.40 mmol) and TMEDA (0.8 mmol) in 8 mL of dry THF at −98°C (methanol/liquid nitrogen bath) under $N_2$ was reacted with *s*-BuLi (0.60 mmol, 1.2 M in cyclohexane). The resulting orange mixture was stirred for 30 min at −98°C. Then, the solution was treated at −98°C with the electrophile (0.60 mmol), added at once, neat if liquid or as solution in 2 mL of THF if solid. The resulting reaction mixture was allowed to warm up to room temperature and finally quenched with saturated aq. $NH_4Cl$, poured into 20 mL of saturated brine, extracted with $Et_2O$ (3×10 mL), dried ($Na_2SO_4$), and evaporated under reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt 7-8/3-2) to give the corresponding α-substituted oxirane showing the following data.

**4.2.1. (1*S*,4′*S*)+(1*R*,4′*S*)-1-Deutero-2-methyl-1-(4-isopropyl-4,5-dihydrooxazol-2-yl)-1,2-epoxypropane (3a-D+4a-D).** Oil (95%), (>95% D), dr 1:1, $^1$H NMR (500 MHz) $\delta$: 0.83 (d, *J*=6.7 Hz, 3H, **4a**-**D**), 0.85 (d, *J*=6.7 Hz, 3H, **3a**-**D**), 0.90 (d, *J*=6.7 Hz, 3H, **4a**-**D**), 0.92 (d, *J*=6.7 Hz, 3H, **3a**-**D**), 1.34 (s, 3H, **4a**-**D**), 1.36 (s, 3H, **4a**-**D**+3H, **3a**-**D**), 1.38 (s, 3H, **3a**-**D**), 1.65–1.90 (m, 1H **4a**-**D**+1H **3a**-**D**), 3.96–3.98 (m, 2H **4a**-**D**+2H **3a**-**D**), 4.23–4.28 (m, 1H, **4a**-**D**+1H, **3a**-**D**). GC-MS *m*/*z* (rel. int.) **3a**-**D**: 184 ($M^+$, 3), 143 (22), 115 (32), 84 (100). GC-MS *m*/*z* (rel. int.) **4a**-**D**: 184 ($M^+$, 3), 143 (22), 115 (32), 84 (100).

**4.2.2. (2*S*,4′*S*)+(2*R*,4′*S*)-2-Deutero-4-isopropyl-2-(1-oxaspiro[2.5]oct-2-yl)-4,5-dihydrooxazole (3b-D+4b-D).** Oil (95%), (73% D), dr 1:1, $^1$H NMR (500 MHz) $\delta$: 0.81 (d, *J*=6.8 Hz, 3H, **3b**-**D**), 0.84 (d, *J*=6.8 Hz, 3H, **4b**-**D**), 0.87 (d, *J*=6.8 Hz, 3H, **3b**-**D**), 0.91 (d, *J*=6.8 Hz, 3H, **4b**-**D**), 1.35–1.75 (m, 11H, **3b**-**D**+11H, **4b**-**D**), 3.36 (s, 1H, **3b**-**D**), 3.38 (s, 1H, **4b**-**D**), 3.85–4.05 (m, 2H, **3b**-**D**+2H, **4b**-**D**), 4.17–4.25 (m, 1H, **3b**-**D**+1H, **4b**-**D**). GC-MS *m*/*z* (rel. int.) **3b**-**D**: 224 ($M^+$, 5), 207 (20), 143 (18), 124 (59), 81 (100). GC-MS *m*/*z* (rel. int.) **4b**-**D**: 224 ($M^+$, 5), 207 (22), 143 (23), 124 (55), 81 (100).

**4.2.3. (4*S*,2′*S*,3′*R*)-(−)-2-Deutero-4-isopropyl-2-(3-phenyloxiranyl)-4,5-dihydrooxazole (3d-D).** White solid mp 76–78°C (hexane) (90%), (>98% D), $[\alpha]_D$=+66 (*c* 1, $CHCl_3$), $^1$H NMR (300 MHz) $\delta$: 0.88 (d, *J*=6.5 Hz, 3H), 0.97 (d, *J*=6.7 Hz, 3H), 1.75 (octet, *J*=6.7 Hz, 1H), 3.90–4.13 (m, 2H), 4.18 (s, 1H), 4.33 (dd, *J*=8.0, 9.1 Hz, 1H), 7.20–7.40 (m, 5H). GC-MS *m*/*z* (rel. int.): 232 ($M^+$, 7), 202 (8), 173 (18), 132 (100).

**4.2.4. (4*S*,2′*R*,3′*R*)-(−)-2-Deutero-4-isopropyl-2-(3-phenyloxiranyl)-4,5-dihydrooxazole (3f-D).** Oil (10%), (>98% D), $\alpha_D^{20}$=−63 (*c* 0.9, $CHCl_3$), $^1$H NMR (500 MHz) $\delta$: 0.61 (d, *J*=6.7 Hz, 3H), 0.72 (d, *J*=6.7 Hz, 3H), 1.35 (octet, *J*=6.7 Hz, 1H), 3.65–3.78 (m, 2H), 3.97–4.05 (m, 1H), 4.24 (s, 1H), 7.20–7.50 (m, 5H). GC-MS *m*/*z* (rel. int.): 232 ($M^+$, 7), 215 (14), 173 (29), 132 (100), 116 (13).

**4.2.5. (2*S*,4′*S*)+(2*R*,4′*S*)-4-Isopropyl-2-(2-methyl-1-oxaspiro[2.5]oct-2-yl)-4,5-dihydrooxazole (6a+6b).** Oil (58%), dr 1:1. Inseparable mixture of diastereoisomers. $^1$H NMR (300 MHz) $\delta$: 0.86 (d, *J*=6.8 Hz, 3H), 0.88 (d, *J*=6.6 Hz, 3H), 0.93 (d, *J*=6.8 Hz, 3H), 0.94 (d, *J*=6.6 Hz, 3H), 1.55 (s, 3H), 1.56 (s, 3H), 1.40–1.82 (m, 11H, **6a**+11H, **6b** overlapping singlets at $\delta$ 1.55 and 1.56), 3.92–4.10 (m, 2H, **6a**+2H, **6b**), 4.20–4.30 (m, 1H, **6a**+1H, **6b**). $^{13}$C NMR (75 MHz) $\delta$: 17.3, 18.2, 18.9, 25.1, 25.7, 30.4, 31.3, 32.4, 32.6, 64.9, 67.0, 67.1, 70.2, 72.3, 72.7, 166.1. GC-MS *m*/*z* (rel. int.): 237 ($M^+$, 2), 194 (10), 156 (15), 124 (100), 81 (62). FT-IR (film) $cm^{-1}$: 2936, 2860, 1671 (C=N), 1449, 1265, 715.

**4.2.6. (2*S*,4′*S*)/(2*R*,4′*S*)-2-[2-(4-Isopropyl-4,5-dihydrooxazol-2-yl)-1-oxaspiro[2.5]oct-2-yl]propan-2-ol (7a/7b).** The two diastereoisomers were separated by column chromatography (silica gel, petroleum ether/AcOEt: 6:4). Spectroscopic data are reported for the two isolated compounds on the basis of their retention factor ($R_f$) on TLC. Their absolute configuration could not be assigned. First eluted diastereomer ($R_f$ 0.6): oil (41%), $\alpha_D^{20}$=−29 (*c* 1, $CHCl_3$), $^1$H NMR (300 MHz) $\delta$: 0.87 (d, *J*=6.6 Hz, 3H), 0.95, (d, *J*=7.1 Hz, 3H), 1.27, (s, 3H), 1.47 (s, 3H), 1.40–1.80 (m overlapping s at $\delta$ 1.47, 8H), 1.82–2.20 (m, 3H), 2.49 (br. s, exchanges with $D_2O$, 1H), 3.80–4.00 (m, 2H), 4.20–4.30 (m, 1H). $^{13}$C NMR (75 MHz) $\delta$: 18.6, 19.4, 24.9, 25.1, 25.3, 25.8, 29.1, 29.7, 33.2, 68.7, 69.8, 69.9, 70.1, 72.5, 163.6 (C=N). MS (ESI) *m*/*z*: 282 (100) $[M+H]^+$, 224 (57) $[M-58]^+$. FT-IR (film) $cm^{-1}$: 3431 (OH), 3054, 2930, 1659 (C=N), 1452, 1023, 737. Second eluted diastereomer ($R_f$ 0.5): oil (41%), $\alpha_D^{20}$=−36 (*c* 1, $CHCl_3$), $^1$H NMR (300 MHz) $\delta$: 0.90 (d, *J*=6.0 Hz, 3H), 1.00 (d, *J*=6.5 Hz, 3H), 1.30 (s, 3H), 1.51 (s, 3H), 1.20–1.80 (m, 10H), 1.90–2.10 (m, 1H), 2.45 (br s, exchanges with $D_2O$, 1H), 3.80–4.00 (m, 2H), 4.20–4.30 (m, 1H). $^{13}$C NMR (75 MHz) $\delta$: 19.0, 19.6, 24.8, 25.0, 25.1, 28.9, 29.4, 29.9, 33.0, 33.3, 68.8, 70.0, 70.4, 73.1, 163.7 (C=N). MS (ESI) *m*/*z*: 282 (100) $[M+H]^+$, 224 (57) $[M-58]^+$. FT-IR (film) $cm^{-1}$: 3538 (OH), 3054, 2961, 1664 (C=N), 1467, 1265, 1002, 737.

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6. Oxazolinyloxiranes **3a**,**b** could be assigned the *S* configuration at the oxiranyl stereogenic centre by analogy to the oxazolinyloxiranes previously prepared by such a methodology, see Ref. 5.
7. The diastereomeric mixture of **3c**-**D** and **4c**-**D** (except for the oxirane proton) shows the same $^1$H NMR of the diastereomeric mixture prepared as reported in Ref. 8.
8. The reaction of lithiated 2-chloromethyl-2-oxazoline with carbonyl compounds proceeds with low stereoselectivity, see: Florio, S.; Capriati, V.; Luisi, R.; Abbotto, A.; Pippel, D. J. *Tetrahedron* **2001**, *57*, 6775–6786.
9. All the four diastereomeric oxazolinyloxiranes **3d**–**g** were isolated (dr >99:1, ee >99%, from GLC analysis) by preparative HPLC and fully characterized. The relative *trans*/*cis* configuration to **3d**–**g** and **3e**,**f** was ascertained on the basis of the proton–proton coupling constant values ($^3J_{HH(trans)}<^3J_{HH(cis)}$). Oxazoliniloxirane **3d** was the only one with a known absolute configuration by X-ray analysis (see Ref. 4b) and was used as reference to determine those of the remaining diastereomeric oxazolinyloxiranes **3e**–**g**. It is worth pointing out that *trans*-**3d** and **3g** exhibit almost identical $^1$H NMR spectra but have different optical rotations (see Section 4), therefore **3g** should have a (4*S*,2′*R*,3′*S*) configuration. The latter also derive from an α-epimerization involving lithiated *cis*-**3e** whose absolute configuration should be therefore (4*S*,2′*S*,3′*S*). The last diastereomer *cis*-**3f**, by exclusion, should have necessarily a (4*S*,2′*R*,3′*R*) configuration.
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