A Stereospecific Synthesis of Oxazolinyloxiranes[⊥]

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Lithiooxiranes **3a** and **3b**, generated by deprotonation of oxiranes **2a** and **2b** with *s*-BuLi at −100 °C in Et_2O, were found to be chemically very stable. *trans*-Lithiooxirane **3a** was also configurationally stable and reacted stereospecifically with electrophiles to give **4a**−**k**. In contrast, *cis*-lithiooxirane **3b** was found to be configurationally much less stable and reacted with electrophiles affording mixtures of diastereomers **4**, **7**, and **8**. After only a very short reaction time, **3b** too reacted with electrophiles highly stereospecifically. Deprotonation−deuteration and deprotonation−alkylation of chiral oxazolinyloxiranes **12a** and **12b** to give oxiranes **12c** and **12d** were also examined. Semiempirical and ab initio calculations were carried out in an effort to explain the observed stereochemistry.

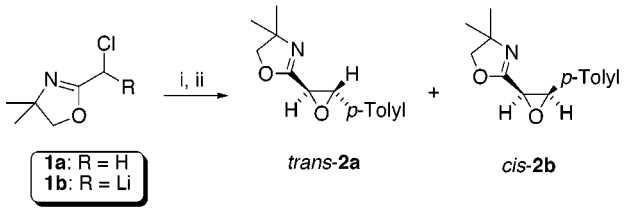
Introduction

Oxazolinyloxiranes are potentially useful synthetic intermediates. In principle, they could be transformed into a variety of useful substances through the synthetic elaboration of either the oxazoline or oxirane rings.[1,2] There are two synthetic procedures to oxazolinyloxiranes that have been recently published, and both were from our laboratory. The first one was a Darzens reaction of azaenolates of chloroalkyloxazolines with carbonyl compounds,[3a,b] while the second one was based on the deprotonation−alkylation sequence of simpler and more easily available oxazolinyloxiranes.[4a,b] Herein, we report a stereospecific synthesis of trisubstituted oxiranes that is based on the deprotonation−alkylation of stereodefined simpler oxazolinyloxiranes.

Results and Discussion

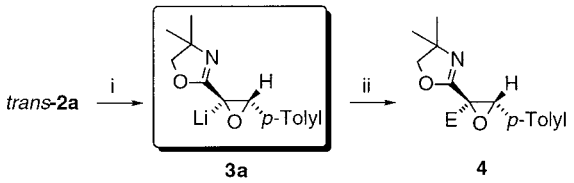
The *trans*- and *cis*-oxazolinyl *p*-tolyloxiranes **2a** and **2b** were prepared through the Darzens reaction of lithiated 2-chloromethyl-4,4-dimethyloxazoline **1b** with *p*-tolualdeyde, as reported[3a,4b] (Scheme 1). Treatment of *trans*-oxazolinyl *p*-tolyloxirane **2a** with *s*-BuLi/TMEDA in Et_2O at −100 °C gave a deep red solution likely to be ascribed to the lithiooxirane **3a**, which was stable for hours at low temperature (Scheme 2). Such a stability has to be attributed to the electron-withdrawing effect of the oxazolinyl group.

Scheme 1[a]



[a] Reagents and conditions: (i) LDA, THF, −100 °C; (ii) *p*-tolylCHO.

Scheme 2[a]



a	E: CH_3	(5 min, 75 %, dr 95:5)[b]
		(2 h, 75 %, dr 95:5)[b]
b	E: CH_2CH_3	(70 %, dr >99:1)
c	E: D	(72 %, 100 % D, dr >99:1)
d	E: $CH_2CH{=}CH_2$	(73 %, dr >99:1)
e	E: $CH_2CH{=}C(CH_3)_2$	(70 %, dr >99:1)
f	E: $[CH_3(CH_2)_3]_3Sn$	(63 %, conv. 90 %, dr 90:10)

[a] Reagents and conditions: (i) *s*-Buli/TMEDA, Et_2O, −100 °C; (ii) E^+. [b] Determined by GC analysis.

The trapping reaction of **3a** with electrophiles furnished trisubstituted oxiranes **4** in good yields (Scheme

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⊥ This paper is dedicated to Prof. A. I. Meyers for his outstanding and fundamental contribution to the chemistry of oxazolines

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(1) Meyers, A. I. *J. Heterocycl. Chem.* **1998**, *35*, 991−1002.

(2) (a) Rao, A. S.; Paknikar, S. K.; Kirtane, J. G. *Tetrahedron* **1983**, *39*, 2323−2367. (b) Doris, E.; Dechoux, L.; Mioskowski, C. *Synlett* **1998**, 337−343.

(3) (a) Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **1996**, *37*, 4781−4784. (b) Florio, S.; Capriati, V.; Luisi, R.; Abbotto, A. *Tetrahedron Lett.* **1999**, *40*, 7421−7425.

(4) (a) Florio, S.; Capriati, V.; Di Martino, S. *Tetrahedron Lett.* **1998**, *39*, 5639−5642. (b) Florio, S.; Capriati, V.; Di Martino, S.; Abbotto, A. *Eur. J. Org. Chem.* **1999**, 409−417.

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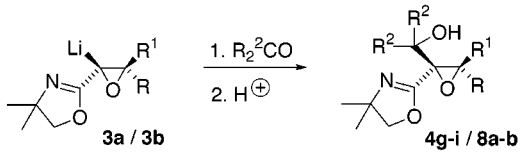
2). The reaction was highly stereospecific, taking place with almost complete retention of configuration (dr = 99:1 to 90:10) at the α carbon, thus indicating that oxiranyllithium **3a** is configurationally stable.[5a,b] This finding substantially conforms with the observation that the C−Li bonds of epoxyalkyllithiums are polar yet covalent in character.[5b] The observed diastereoselectivity was not time-dependent. Indeed, the methylation of **3a** at different reaction times (5 min and 2 h) gave **4a** with the same diastereomeric enrichment (dr = 95:5). The *trans* configuration of **4a** is in accordance with that previously reported.[4b] Equally highly stereospecific was the reaction of **3a** with other electrophiles (EtI, MeOD, allyl bromide, 3,3-dimethylallyl bromide, Bu_3SnCl) to give compounds **4b**−**f**. Oxirane **4b** was assigned the configuration on the basis of the very small long-range $^3J_{CH}$ coupling constant ($^3J_{CH_2-H} \approx 0$ Hz) between the oxirane *β*-hydrogen and the hydrogens of the methylene group of the substituent on the α-carbon. Such evidence suggests that these groups are on opposite sides, as previously reported for **4a**[4b] and similar trisubstituted epoxides.[6a,b] We also noted that in *Z* epoxides (see below) (in which the oxazoline and the *p*-tolyl rings are on the same side) the two geminal methyls and protons of the oxazoline ring absorb in all cases at higher field than those of the *E* isomers (Δppm = 0.3−0.4).[7] A similar shielding effect was observed for all these protons in the case of epoxides **4c**−**f** that, therefore, for the above reasons, should have the *E* configuration. A NOESY phase-sensitive spectrum was also run for **4d**; cross-peaks between aromatic protons and the two allylic and vinylic CH_2 (testifying an *E* configuration) confirmed the above considerations.

The reaction of **3a** with ketones again occurred stereospecifically and provided potentially useful hydroxyalkyl oxazolinyloxiranes **4g**, **4h**, and **4i** in good yields (Table 1), while the reaction with aldehydes led to diastereomeric mixtures of *syn*/*anti*[8] hydroxyalkyl oxazolinyloxiranes **4j** and **4k** (Table 2).

Attempts to capture **3a** with 2-chloromethyl-4,4-dimethyloxazoline (**1a**) that would lead to the dioxazolinyloxirane **5** (Chart 1) failed. Quenching of the reaction mixture with saturated aqueous NH_4Cl afforded **2a** and dioxazolinylethene **6**[9] (60%) (Chart 1). It is likely that oxiranyllithium **3a** abstracts a proton from **1a** to give lithiated derivative **1b**, which in turn reacts with itself or with its precursor to produce the homocoupling product **6**.[10]

The reaction of oxiranyllithium **3b** (Scheme 3), generated by deprotonation of the *cis*-oxazolinyl oxirane **2b** (*s*-BuLi/TMEDA, Et_2O at −100 °C), was not stereoselective.

Table 1. Reactions of Oxiranyllithiums 3a and 3b with Ketones



compd		yield (%)[a]	conv (%)[b]	dr[c]
4g	R = H; R^1 = *p*-tolyl; $R^2 = CH_2CH_3$	80	60	>99:1[d,e]
4h	R = H; R^1 = *p*-tolyl; $R^2 = (CH_2)_5$	70	68	96:4[e]
4i	R = H; R^1 = *p*-tolyl; R^2 = Ph	60	>95	>99:1[d,e]
8a	R = *p*-tolyl; R^1 = H; $R^2 = CH_2CH_3$	60	86	95:5[f,g,h]
8b	R = *p*-tolyl; R^1 = H; R^2, $R^2 = (CH_2)_5$	71	83	90:10[f,g,h]

[a] Based on converted material. [b] This value arises from the following ratio: (initial reacting moles − residual moles)/initial reacting moles. [c] Diastereomeric ratio. [d] Determined by ^{1}H NMR spectroscopy; only one diastereomer in the ^{1}H NMR spectrum of the crude product. [e] Refers to the *E*/*Z* ratio. [f] Evaluated by GC analysis. [g] Inseparable mixture of diastereomers. [h] Refers to the *Z*/*E* ratio.

Indeed, deuteration of **3b** with D_2O (5 min after its generation or later) afforded deuterated oxiranes **7c** and **4c** with a reasonable diastereoselection (dr **4c**:**7c** = 17:83), while the alkylation with MeI and EtI furnished **7a**,**b** and **4a**,**b** with poor (dr **4a**:**7a** = 60:40) or no stereoselection (dr **4b**:**7b** = 50:50), respectively. Comparable results were obtained when the deprotonation−methylation reaction of **2b** was carried out in hexane or toluene. In THF, the diastereomeric ratio was markedly in favor of the isomer **4a** (dr **4a**:**7a** = 90:10). These data clearly indicate that oxiranyllithium **3b**, contrary to what was found for **3a**, is not configurationally stable.

The lack of stereospecifity of the reaction of organolithium *cis*-**3b** could be ascribed to the fact that it tends to convert rapidly into the more stable *trans* isomer **3a**, and this might be attributed to the strain created in forcing the oxazolinyl group and the aryl group *cis* on the oxirane ring.[5a] Thus, when the electrophile is added to the reaction mixture some time after the deprotonation has occurred, it is the **3a** + **3b** mixture that reacts, affording mixtures of diastereomers. In particular, the methylation reaction of **3b** with MeI at different times after its generation (5 min, 2 and 8 h) afforded diastereomeric mixtures with **4a**:**7a** ratio ranging from 60:40 to 70:30 and 80:20, respectively. This evidence further supports the suggestion that *cis*-**3b** tends to convert into *trans*-**3a**. Moreover, when the oxiranyllithium **3b** was treated with the electrophile immediately after its generation, the trapping occurred in a good to highly stereoselective way (retention of configuration). Indeed, treatment of *cis*-**2b** with *s*-BuLi/TMEDA in Et_2O at −100 °C in the presence of MeI (Barbier's technique) afforded **7a** (dr = 78:22) with prevalent retention of configuration.

(5) That stabilized oxiranyllithiums are, in general, configurationally stable has been stressed by other authors. (a) Molander, G. A.; Mautner, K. *J. Org. Chem.* **1989**, *54*, 4042−4050. (b) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1990**, *55*, 4835−4840.

(6) (a) Kingsbury, C. A.; Durham, D. L.; Hutton, R. *J. Org. Chem.* **1978**, *43*, 4696−4700. (b) Florio, S.; Capriati, V.; Russo, V. *Gazz. Chim. Ital.* **1997**, *127*, 587−595.

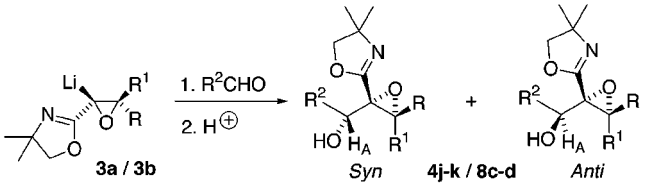
(7) *Z* isomers: 2 × CH_3, δ 0.94−1.02 ppm; CH_2O, 3.50−3.70 ppm. *E* isomers: 2 × CH_3, δ 1.29−1.30 ppm; CH_2O, 3.90−4.00 ppm.

(8) The convention employed for describing *syn* and *anti* diastereomers is as follows: if the main chain is written in an extended (zigzag) conformation, the diastereomer that has the oxiranyl ring and the hydroxy group both projecting either forward (bold bonds) or away from the viewer (dashed bonds) is called *syn*. The assignment of *syn* (or *anti*) stereochemistry was made on the basis of the characteristic resonance of the H_a proton (see Table 2) that in the case of the *anti* isomers was always shifted downfield compared to those of the *syn* isomers, as reported for similar epoxy alcohols. See ref 4b and references therein.

(9) The *E* configuration of **6** was established by considering the doublet of doublets arising from ^{13}C satellites for the peak at δ 3.91 in its ^{1}H NMR spectrum. The larger splitting due to a $^1J_{13C-H}$ is 168.4 Hz, while the smaller one due to a $^3J_{H-H}$ splitting is 16.5 Hz. The magnitude of the latter gives evidence for a *trans* arrangement of the vinylic hydrogens.

(10) In ref 3a we reported that lithiated 2-chloromethyl-4,4-dimethyloxazoline **1b** is rather unstable and tends to react with its precursor **1a** to give homocoupling ending up with the formation of alkene **6** (Chart 1) upon HCl elimination. At present it appears more convincing that **6** originates from a coupling reaction between two lithiated species **1b**, which has the carbenoid character. A deeper investigation into the fate of **1b** in the absence of an external electrophile is under way in our lab and will be published in due course.

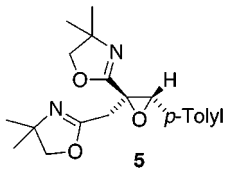
Table 2. Reactions of Oxiranyllithiums 3a and 3b with Aldehydes



compd		overall yield (%)[a]	dr *E*/*Z*	dr *syn*/*anti* (*E*)[b]	dr *syn*/*anti* (*Z*)[b]
4j	R = H; R^1 = *p*-tolyl; R^2 = CH_3	55[c]	>99:1[d]	1.1:1[e,f]	
4k	R = H; R^1 = *p*-tolyl; R^2 = Ph	69[c]	>99:1[d]	1:1[e,g]	
8c	R = *p*-tolyl; R^1 = H; R^2 = CH_3	64[h]	12:88[e]	1.82:1[e,f]	2.7:1[e,i]
8d	R = *p*-tolyl; R^1 = H; R^2 = Ph	95[j]	12:88[e]	2.2:1[e,g]	2.3:1[e,i]

[a] Based on converted material and referring to all possible stereoisomers. [b] *syn*/*anti* diastereomeric ratio referring to the *E* (or *Z*) epoxyalcohol. [c] Conversion, 90%. [d] Determined by ^{1}H NMR spectroscopy; only one diastereomer in the ^{1}H NMR spectrum of the crude product. [e] Determined by GC analysis. [f] Separable mixture of diastereomers: Et_2O/petroleum ether = 3:2. [g] Separable mixture of diastereomers: Et_2O/petroleum ether = 1:1. [h] Conversion, 70%. [i] Inseparable mixture of diastereomers. [j] Quantitative conversion.

Chart 1



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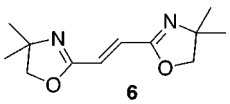
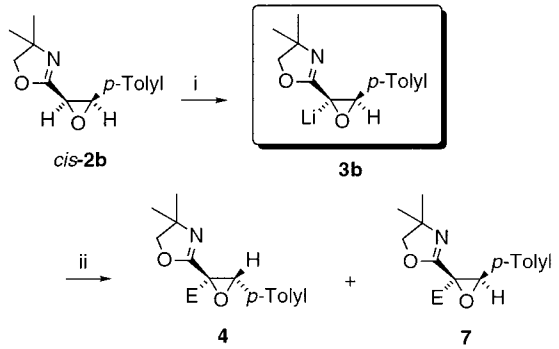


6

Scheme 3[a]



a E: CH_3 (71 %, *E*:*Z* = 60:40)[b]

b E: CH_2CH_3 (70 %, *E*:*Z* = 50:50)[c]

c E: D (75 %, 100 % D, *E*:*Z* = 17:83)

[a] Reagents and conditions: (i) *s*-Buli/TMEDA, Et_2O, −100 °C; (ii) E^+. [b] Separable mixture of diastereomers: silica gel, hexane/AcOEt = 6:4. [c] Separable mixture of diastereomers: silica gel, Et_2O/petroleum ether = 6:4.

Moreover, the reaction of **3b** with carbonyl compounds took place with retention of configuration (ranging from 88% to 95%) producing hydroxyalkyl oxazolinyloxiranes **8a**−**d** (Tables 1 and 2).

A possible explanation for the above results relies on the assumption that (a) oxiranyllithium *trans*-**3a** is configurationally quite stable, whereas *cis*-**3b** is not; (b) *cis*-**3b** tends to transform into *trans*-**3a**, establishing an equilibrium that is markedly shifted toward the latter, more stable compound; (c) the reaction of *cis*-**3b** with the electrophile is faster than that of *trans*-**3a**; in an experiment planned to evaluate the relative reactivities of **3a** and **3b**, the deprotonation of *cis* oxazoline **2b** and *trans* isomer **2a** was examined. Treatment of a 1:1 mixture of **2a** and **2b** first with 0.5 equiv of *s*-BuLi and then with MeI (quenching at different times) led to the expected methylated product (ca. 1:1 *E* + *Z* diastereomeric mixture), the unreacted *trans* isomer **2a,** and the complete consumption of **2b**. On this basis, one must conclude that the deprotonation of **2b** is faster than that of **2a** and lithiooxirane **3b** is more reactive than **3a**. There are precedents of *cis* oxiranes that undergo deprotonation faster than the *trans* counterparts.[11a,b]

The deprotonation−alkylation of chiral nonracemic oxazolinyloxiranes was also investigated. Optically pure oxazolinyloxirane **10** (Scheme 4) was prepared by chlorination of the corresponding 2-methyl-4-methoxymethyl-5-phenyloxazoline **9**, commercially available, with *t*-BuOCl.[3b,12] Treatment of **10** with dibutylboron triflate and *N*,*N*-diisopropylethylamine (Bu_2BOTf/*i*-Pr_2NEt) furnished the boron azaenolate **11a**, which without isolation was reacted with 4,4′-dimethylbenzophenone to give oxazolinyloxirane **12a** (dr = 93:7).[3b] The stereochemistry at the α-carbon of **12a** was ascertained to be *S* by X-ray analysis.[13] Treatment of **12a** with *s*-BuLi/TMEDA at −100 °C in Et_2O followed by the addition of D_2O (10 min) gave deuterated oxirane **12c** (dr = 76:24). On the other hand, the deprotonation−methylation of **12a** afforded methylated oxirane **12d** (dr = 80:20). Therefore, the stereochemistry of **12a** was substantially retained in the derivatives **12c** and **12d**.[14] In contrast, the deprotonation−deuteration of **12b** (dr = 95:5) (prepared by

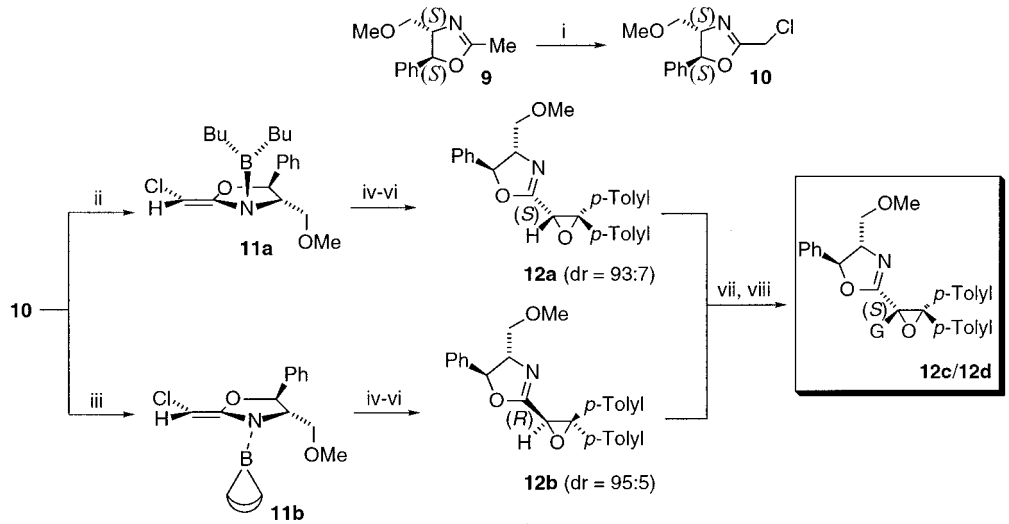
(11) (a) Satoh, T. *Chem. Rev.* **1996**, *96*, 3303−3325. (b) Mori, Y. *Rev. Heteroatom Chem.* **1997**, *17*, 183−211.

(12) Compound **10** could also be prepared by ortho ester condensation directly from triethyl orthochloroacetate (Kamata, K.; Sato, H.; Takagi, E.; Agata, I.; Meyers, A. I. *Heterocycles* **1999**, *51*, 373−378) or by condensing (1*S*,2*S*)-(+)-1-phenyl-2-amino-1,3-propanediol (Aldrich) with ethyl acetimidate hydrochloride (Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567−576) and finally chlorination with *t*-BuOCl (Mintz, M. J.; Walling, C. *Organic Syntheses*; Wiley: New York, 1973; Collect. Vol. V, p 184−197).

(13) Crystallographic data for compound **12a** have been deposited at the Cambridge Crystallographic Data Centre (deposition number CCDC-147476). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk]. Crystallographic data and geometry tables for compound **12a** have been also reported as Supporting Information; all diagrams and calculations were performed using maXus (Nonius, Delft & MacScience, Japan).

(14) Generally, β,β-diaryl oxazolinyl epoxides of *S* and *R* configuration exhibit a characteristic doublet for each of the two diastereomeric oxazolinyl ring hydrogens at C-5 in the range of 5.0−5.1 and 5.18−5.20 ppm and a doublet of doublets for each of the two methylenic hydrogens in the side chain of the oxazolinyl ring in the range of 3.40−3.55 and 3.20−3.40 ppm, respectively. See also ref 3b.

Scheme 4[a]



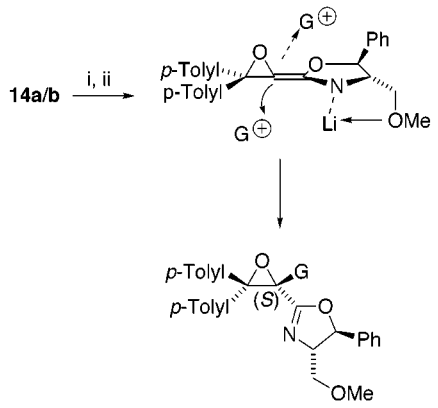
12c G = D (80%); dr = 76:24[b,c] **12c** G = D (75 %); dr = 70:30[b,c]

from **12a** from **12b**

12d G = Me (71%); dr = 80:20 **12d** G = Me (68 %); dr = 80:20

[a] Reagents and conditions: (i) *t*-BuOCl/CCl_4; (ii) Bu_2BOTf/*i*-Pr_2NEt; (iii) 9-BBNOTf/*i*-Pr_2NEt; (iv) (*p*-Tolyl)$_2CO$; (v) H^+; (vi) NaOH/*i*-PrOH; (vii) *s*-Buli/TMEDA, Et_2O, −100 °C; time after deprotonation: 10 min; (viii) G^+. [b] dr = 92:8 after crystallization from hexane. [c] 100% D.

Scheme 5[a]



the reaction of boron azaenolate **11b** with 4,4′-dimethylbenzophenone)[3b] provided deuterated oxirane **12c** (dr = 70:30), while the deprotonation−methylation sequence afforded oxirane **12d** (dr = 80:20). Therefore, starting from **12b**, the original stereochemistry is substantially lost in the related deuterated and methylated compounds (Scheme 4).

The observed preferential formation of *S*-configurated substituted epoxides at Cα, starting from the above optically enriched oxiranes, could be rationalized by assuming that the electrophile could approach the azaenolate either from the top or from the bottom but with a preference from the side opposite to the phenyl group, via a transition state in which the lithium is coordinated by the methoxy group (Scheme 5).

A similar lithioenamine, as depicted in Scheme 5, has already been postulated in the asymmetric oxazoline ketenimine rearrangement.[15a] Moreover, a ^{13}C and ^{15}N NMR investigation performed on certain lithiated alkyloxazolines has shown that a considerable amount of the negative charge resides on the oxazoline nitrogen atom.[15b] We reasoned, at this stage, that it could be useful to calculate the relative stability of the organolithiums **3a** and **3b** and the interconversion barrier energy. We therefore undertook an ab initio and semiempirical computational investigation aimed at computing the relative energies of the two geometric isomers of oxiranyllithium **3** (namely, *trans*-**3a** and *cis*-**3b**) and searching for a low energy transition state or intermediate that could account for the *cis*-*trans* interconversion.

Ab Initio and Semiempirical Calculations

Computational Details. All ab initio calculations used either the GAUSSIAN 94[16] or GAUSSIAN 98[17] program packages and the standard basis set 6-31+G* and 6-311+G*. Because of the size and point group symmetry (C_1) of the molecules under investigation, we carried out full geometry optimizations and frequency calculations at the HF/6-31+G* level of theory. To introduce electron correlation in the computation of the energetics, we performed single-point calculations[18] using the density functional theory (DFT)[19] at the B3LYP/6-311+G*//HF/6-31+G* level of theory.[20] Semiempirical

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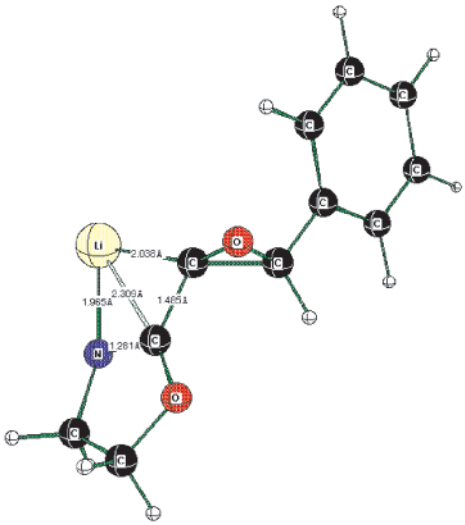
calculations used the MOPAC 6.0 program,[21,22] with the keywords PM3, EF, and PRECISE. Stationary points were characterized as minima (no imaginary frequencies) by frequency analysis, both at the ab initio (HF) and semiempirical level. Zero-point vibrational energies of HF calculations were scaled by an empirical factor of 0.91.[23] Calculations were partially carried out at the Cineca Supercomputer Center in Bologna (Italy) on SGI Origin 3800 and IBM SP RS/6000 Power3 machines.

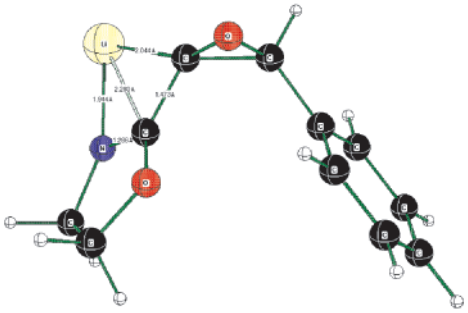
Ab initio computations were carried out for model isomers *trans*-**3a′** and *cis*-**3b′**, where methyl groups at the 4 position of the oxazolinyl and in the *para* position of the phenyl rings in **3a** and **3b** were replaced by hydrogen atoms (Figure 1). Such a replacement does not introduce any significant effect on the geometries and relative energies of the two isomers, as ascertained a posteriori.

Results. Ab initio geometry optimizations resulted in global minimum-energy structures for isomers *trans*-**3a′** and *cis*-**3b′**, each charaterized by zero imaginary frequencies. Optimized structures, with selected geometric parameters, are presented in Figure 1. PM3 computations have been shown to reproduce with good accuracy geometries of organolithium compounds as compared to experimental data and high-level ab initio and DFT methods.[24] However, the corresponding PM3 energies are not always as good. For comparison, PM3 optimized structures of lithium salts **3a** and **3b** are shown in Figure 2.

Structures of the lithium salts very closely resemble those of the precursors, *trans*-**2a** and *cis*-**2b**. In all of the ab initio and PM3 optimized structures, the lithium cation bearing carbanionic carbon atom has a distorted sp^3 arrangement in order to allow a stabilizing intramolecular coordination between lithium and the oxazoline nitrogen atom and π bond. A comparison of PM3 selected geometric parameters between the lithium salt **3a** and its precursor is reported in Table 3. With the exception of parameters involving the cation, lengths and angles



3a'. Li-C(α)-C(2) 80°
Li-N-C(2) 88°
Li-N-C(2)-C(α) −9°
Li-C(α)-C(β)-C(2) −110°



3b'. Li-C(α)-C(2) 79°
Li-N-C(2) 87°
Li-N-C(2)-C(α) −17°
Li-C(α)-C(β)-C(2) −107°

Figure 1. RHF/6-31+G* optimized structures of oxiranyllithiums **3a′** and **3b′**.

are similar in the carbanion and in its precursor. The formation of the negative charge onto one of the oxiranyl carbon atoms (Cα) leads only to a small lengthening of the bond C(2)−N and shortening of the bond C(2)−C(α), likely due to an unfavored interaction between the carbanionic heterocyclic orbitals having different symmetry.

DFT energetics of the two lithium salts **3a′** and **3b′** are presented in Table 4. For sake of comparison, Table 4 shows PM3 relative energies of compounds **3a** and **3b**. Although the two isomers are close in energy, the *cis*-**3b′** isomer is less stable than the *trans*-**3a′** by about 1.5 kcal/mol, likely as a result of a destabilizing interaction between the heterocyclic and phenyl rings.

Every attempt to locate a transition state structure in the interconversion process between the *trans*-**3a′** and *cis*-**3b′** isomers proved to be very difficult at the Hartree−Fock level.[24d] Computational limitations prevented us

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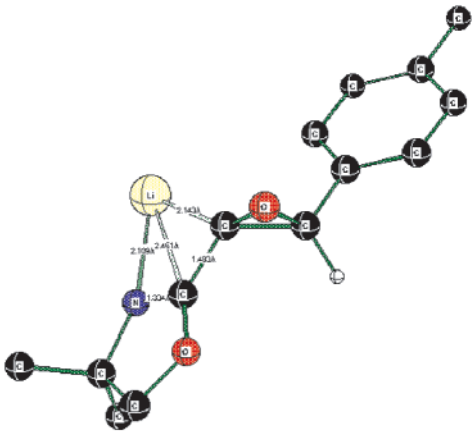
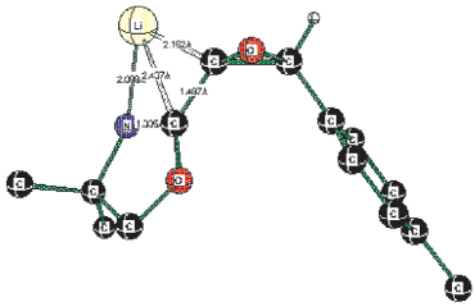


3a. Li-C(α)-C(2) 83°
Li-N-C(2) 88°
Li-N-C(2)-C(α) −10°
Li-C(α)-C(β)-C(2) −110°



3b. Li-C(α)-C(2) 82°
Li-N-C(2) 88°
Li-N-C(2)-C(α) −12°
Li-C(α)-C(β)-C(2) −117°

Figure 2. PM3 optimized structures of oxiranyllithiums **3a** and **3b**.

Table 3. Comparison between Selected Geometric Parameters of Lithium Salt *trans*-3a and Its Precursor *trans*-2a[a,b]

parameter	*trans*-**2a**	*trans*-**3a**
C(2)−N	1.30 Å	1.33 Å
C(2)−O (oxazoline)	1.38 Å	1.36 Å
C(α)−O (oxirane)	1.43 Å	1.42 Å
C(α)−C(*β*)	1.50 Å	1.49 Å
C(2)−C(α)	1.49 Å	1.48 Å
C(2)−C(α)−C(*β*)	121°	121°
H(α)−C(α)−C(*β*)	120°	
Li−C(α)−C(*β*)		132°
C(2)−C(α)−C(*β*)−O (oxirane)	−106°	−108°
H(α)−C(α)−C(*β*)−O (oxirane)	+103°	
Li−C(α)−C(*β*)−O (oxirane)		+142°
H(α)−C(α)−C(*β*)−C(2)	−152°	
Li−C(α)−C(*β*)−C(2)		−110°

[a] Position 2 refers to the oxazoline ring. Positions α and *β* refer to carbon and hydrogen atoms of the oxiranyl ring with respect to the heterocycle. [b] PM3 optimized geometries.

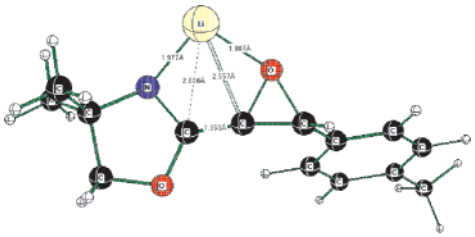
from performing a full ab initio and DFT investigation aimed at locating an intermediate or transition state structure.

At a semiempirical level, different geometries were considered and optimized in the search for a stable form that could act as intermediate or transition state in the *cis*-**3b** and *trans*-**3a** interconversion process. Structure **3I** (Figure 3) was found to be the most stable form, with the lithium gegenion forming a bridge between the oxazolinyl nitrogen and oxiranyl oxygen atoms in an almost planar arrangement. This structure was characterized as a minimum-energy geometry by frequency calculation (keyword FORCE) and is therefore a local minimum-energy intermediate. The energy of the intermediate **3I** is higher than that of the *trans*-**3a** and *cis*-**3b** isomers by 1.8 and 0.9 kcal/mol, respectively. Although PM3 energies are not as accurate as ab initio values, we believe that the sufficiently good agreement between the ab initio and semiempirical data computed for the two lithium salts **3a**−**3a′** and **3b**−**3b′** (see Table 4) makes the overall picture reliable, at least on a qualitative basis (Figure 4).

Table 4. Ab Initio Absolute and Relative Energies and Zero-Point Energies of Oxiranyllithium *trans*-3a′ and *cis*-3b′ (PM3 Relative Energies of Oxiranyllithium *trans*-3a and *cis*-3b Are Reported for Comparison)

			relative energies	
species	E^a	ZPE[b]	DFT[c]	PM3[d]
trans-**3a′**	−638.01530	0.18675	0	0
cis-**3b′**	−638.01310	0.18695	+1.38 (+1.51)	+0.91

[a] Absolute B3LYP/6-311+G*//RHF/6-31+G* energies (Hartrees). [b] Zero-point energy values from HF/6-31+G* calculations (Hartrees). Values were scaled by a factor of 0.91. [c] B3LYP/6-311+G*//RHF/6-31+G* relative energies in kcal/mol. Value in parentheses is zero-point energy corrected. [d] PM3 relative energies in kcal/mol. Values are referred to isomers **3a** and **3b**.



3I. Li-C(α)-C(2) 77°
Li-N-C(2) 99°
Li-N-C(2)-C(α) −4°
Li-C(α)-C(β)-C(2) 126°

Figure 3. PM3 optimized structure of the oxiranyllithium intermediate **3I**.

In conclusion, the *trans*-**3a** isomer is the most stable species, as ascertained by high-level ab initio calculations. Once the *cis*-*trans* equilibrium has been attained, the energetics predict that the *trans* form is highly predominant. From PM3 energetics on structure **3I**, we can postulate that the interconversion barrier is predicted to be as high as a few kcal/mol.

Conclusion

On the basis of the above calculations, the observed stereoselection of the reactions of *trans* and *cis* organolithiums **3a** and **3b** with electrophiles can be accounted for by considering that **3a** and **3b** are in a dynamic equilibrium that tends to shift toward the more stable *trans*-**3a** isomer with the time. Moreover, it has been experimentally proved that *cis*-**3b** is more reactive than *trans*-**3a** isomer. Therefore, while the observed high

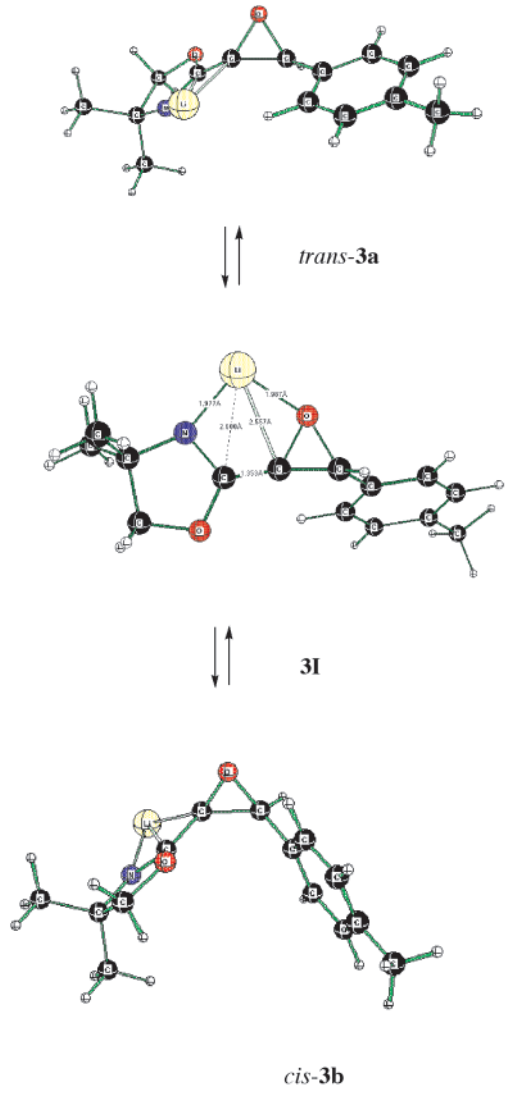


Figure 4. Interconversion process between *trans*-**3a** and *cis*-**3b** through **3I**.

stereospecificity of the reactions of **3a** can be reasonably explained with its configurational stability, the absence of (or very poor) stereoselection of the reactions of **3b** with electrophiles, when the trapping is performed some time after its generation, has to be ascribed to the **3b** → **3a** isomerization. Moreover, the good stereospecificity of the reactions of **3b** with electrophiles, which occurs when the trapping is effected soon after the lithiated intermediate has been generated, is to be ascribed to the fact that the reaction of **3b** with the electrophile is faster than its isomerization to **3a**. Finally, the higher reactivity of **3b** with respect to **3a** could explain the fact that even when the trapping of the lithiated species derived from **2b** is performed after a long time there is still some product derived from **3b**.

All of the oxazolinyloxiranes described in this paper appear to be useful from the synthetic viewpoint as they could be transformed into a variety of other substances just by the elaboration of one or both the oxazolinyl and the oxiranyl rings.

Experimental Section

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. The *trans*- and *cis*-oxazolinyl *p*-tolyloxiranes **2a** and **2b** were prepared as reported.[3a,4b] All other chemicals were of commercial grade (Aldrich) (dibutyboron triflate, solution 1 M in CH_2Cl_2, and 9-borabicyclo[3.3.1]nonyl trifluoromethanesulfonate, 0.5 M in hexanes, were purchased from Fluka) and used without further purification. *tert*-Butyl hypochlorite (*t*-BuOCl) was prepared as reported in ref 12. Petroleum ether refers to the 40−60 °C boiling fraction. A commercial solution of *s*-BuLi (in cyclohexane) from Aldrich was titrated by using *N*-pivaloyl-*o*-toluidine prior to use.[25] For the ^1H and ^{13}C NMR spectra (^1H NMR 90, 200, 300, 500 MHz; ^{13}C NMR 50.3, 125 MHz), $CDCl_3$ was used as solvent. GC−MS spectrometry analyses were performed on a gas chromatograph HP 5890 II (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a mass selective detector operating at 70 eV (EI). Melting points were uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished by UV light (254 nm). Column chromatography was performed by using silica gel (70−230 mesh) with petroleum ether/AcOEt mixture as the eluent. Compounds **4a** and **4b** were separated from **7a** and **7b** by chromatography on silica gel with hexane/AcOEt (6:4) and Et_2O/petroleum ether (6:4) as eluents, respectively. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

Preparation of α-Substituted Oxazolinyl *p*-Tolyloxiranes 4a−k, 7a−c, 8a−d, 12c−d. General Procedure. A solution of **2a** (100 mg, 0.43 mmol) and TMEDA (0.10 mL, 0.65 mmol) in 4 mL of Et_2O at −100 °C (with a methanol/liquid nitrogen bath) and under N_2 was reacted with *s*-BuLi (0.54 mL, 0.65 mmol, 1.2 M in cyclohexane), and the resulting orange mixture was stirred for 15 min at −100 °C. In the case of **2b** and **12a.b**, the incipient anion was stirred at −100 °C for only 10 s. Then, the solution was quenched with the electrophile (0.86 mmol), added at once, and stirred at −100 °C for 1 h. The resulting reaction mixture was finally treated with saturated aqueous 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 = 6−7:4−3) to give the corresponding α-substituted epoxides, which showed the following data.

(*E*)-1,2-Epoxy-2-(4,4-dimethyl-2-oxazolin-2-yl)-1-*p*-tolylpropane (4a): 75%, dr = 95:5, oil. The spectroscopic data of this epoxide and those of the *Z* isomer were reported in ref 4b. Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.21; H, 7.64; N, 5.73.

(*E*)-1,2-Epoxy-2-(4,4-dimethyl-2-oxazolin-2-yl)-1-*p*-tolylbutane (4b): 70%, dr > 99:1, oil. ^1H NMR (300 MHz) δ 0.94 (t, J = 7.3 Hz, 3 H), 1.31 (s, 6 H), 1.48 (dq, ^2J_d = 14.0, ^3J_q = 7.3 Hz, 1 H), 1.72 (dq, ^2J_d = 14.0, ^3J_q = 7.3 Hz, 1 H), 2.33 (s, 3 H), 4.01 and 3.99 (2 × d, AB system, J = 8.1 Hz, 2 H), 4.35 (s, 1 H), 7.12−7.24 (m, 4 H). ^{13}C NMR (50.3 MHz) δ 9.0, 20.6, 21.1, 28.1, 28.2, 61.4, 62.7, 67.7, 79.2, 126.5, 128.7, 131.3, 137.6, 163.1. GC−MS (70 eV) *m*/*z* (%) 259 (2.5, M^+), 244 (4.4), 202 (4.8), 146 (100.0), 119 (12.7), 105 (15.1), 91 (20.0), 57 (78.1), 41 (39.1). FT-IR (film, cm^{-1}) 2971, 1659 (s, CN), 1516, 1463, 1137, 809, 730. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.32; H, 8.18; N, 5.41.

(*E*)-1-Deutero-1,2-epoxy-1-(4,4-dimethyl-2-oxazolin-2-yl)-2-*p*-tolylethane (4c): 72%, 100% D, dr > 99:1, oil. ^1H NMR (90 MHz) δ 1.35 (s, 3 H), 1.38 (s, 3 H), 2.38 (s, 3 H), 4.07 (s, 2 H), 4.15 (s, 1 H), 6.97−7.50 (m, 4 H). GC−MS (70 eV) *m*/*z* (%) 232 (3.7, M^+), 217 (9.5), 177 (13.9), 147 (10.8), 146 (100.0), 121 (10.7), 119 (10.5), 91 (13.8). FT-IR (film, cm^{-1}) 2965, 1655 (s, CN), 1510, 1295, 985, 815. Anal. Calcd for $C_{14}H_{16}DNO_2$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.16; H, 7.66; N, 5.92.

(*E*)-4,5-Epoxy-4-(4,4-dimethyl-2-oxazolin-2-yl)-5-*p*-tolylpent-1-ene (4d): 73%, dr > 99:1, oil. ^1H NMR (300 MHz) δ = 1.29 (s, 3 H), 1.30 (s, 1 H), 2.22 (ddt, J = 14.8, 6.7,1.3 Hz, 1

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H), 2.33 (s, 3 H), 2.48 (ddt, J = 14.8, 6.7,1.3 Hz, 1 H), 3.98 and 4.00 (2 × d, AB system, J = 8.1 Hz, 2 H), 4.37 (s, 1 H), 4.91−5.01 (m, 2 H), 5.71−5.85 (m, 1 H), 7.13−7.23 (m, 4 H). ^{13}C NMR (50.3 MHz) δ 21.1, 28.2, 31.8, 59.9, 62.3, 67.8, 79.4, 118.0, 126.6, 128.8, 131.0, 132.1, 137.8, 163.1. GC−MS (70 eV) m/z (%) 271 (0.1, M^+), 146 (100.0), 119 (11.4), 91 (16.0), 41 (32.2). FT-IR (film, cm^{-1}) 3078, 2966, 1658 (s, CN), 1516, 1135, 1033, 971, 920, 816. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.57; H, 8.01; N, 5.17.

(*E*)-5,6-Epoxy-5-(4,4-dimethyl-2-oxazolin-2-yl)-2-methyl-6-*p*-tolylhex-2-ene (4e): 70%, dr > 99:1, oil. ^{1}H NMR (300 MHz) δ 1.28 (s, 3 H), 1.29 (s, 3 H), 1.37 (s, 3 H), 1.62 (s, 3 H), 2.14−2.21 (m, 1 H), 2.32 (s, 3 H), 2.35−2.43 (m, 1 H), 3.96 and 3.99 (2 × d, AB system, J = 8.2 Hz, 2 H), 4.33 (s, 1 H), 5.11−5.15 (m, 1 H), 7.12−7.24 (2 m, 4 H). ^{13}C NMR (APT, 50.3 MHz) δ 17.8 (*C*H$_3$), 21.2 (*C*H$_3$), 25.8 (*C*H$_3$), 26.8 (*C*H$_2$C═), 28.2 (*C*H$_3$), 28.3 (*C*H$_3$), 60.9, 62.6, 67.7, 79.4 (*C*H$_2$O), 117.6 (*C*H═), 126.6, 128.8, 131.3, 134.8, 137.7, 161.8 (C═N). GC−MS (70 eV) m/z (%) 299 (14.6, M^+), 271 (36.7), 230 (53.2), 203 (21.1), 132 (100.0), 41 (83.4). FT-IR (film, cm^{-1}) 2968, 1659 (s, CN), 1517, 1455, 1126, 1042, 971, 816. Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.59; H, 8.69; N, 4.71.

(*E*)-1,2-Epoxy-1-(4,4-dimethyl-2-oxazolin-2-yl)-2-*p*-tolyl-1-trimethyltinethane (4f): 63%, conv. 90%, dr = 90:10, oil. ^{1}H NMR (500 MHz) δ 0.60−0.71 (m, 6 H), 0.81 (t, J = 7.2 Hz, 9 H), 1.13−1.22 (m, 6 H), 1.23−1.34 (m overlapping singlets at δ 1.28 and 1.26, 6 H), 1.26 (s, 3 H), 1.28 (s, 3 H), 2.32 (s, 3 H), 3.92 and 3.94 (2 × d, AB system, J = 8.0 Hz, 2 H), 4.12 (s, 1 H), 7.10−7.24 (2 m, 4 H). ^{13}C NMR (125 MHz) δ 10.5, 13.6, 21.2, 27.3, 28.6, 59.9, 61.3, 67.2, 79.3, 125.9, 128.9, 134.5, 137.6, 166.8. GC−MS (70 eV) m/z (%) 291 (30.5, ^{120}Sn(Bu)$_3^+$, M^+ − 230), 269 (100.0), 235 (31.2), 213 (22.8), 177 (57.0), 155 (19.7), 121 (20.1), 57 (13.8), 41 (12.4). FT-IR (film, cm^{-1}) 2957, 1644 (s, CN), 1463, 1300, 996, 866, 682. Anal. Calcd for $C_{26}H_{43}NO_2$Sn: C, 60.01; H, 8.33; N, 2.69. Found: C, 60.37; H, 8.65; N, 2.82.

(*E*)-1,2-Epoxy-3-ethyl-2-(4,4-dimethyl-2-oxazolin-2-yl)-1-*p*-tolylpentan-3-ol (4g): 80%, conv. 60%, dr *E*:*Z* > 99:1, oil. ^{1}H NMR (500 MHz) δ 0.80 (t, J = 7.5 Hz, 3 H), 0.89 (t, J = 7.5 Hz, 3 H), 1.29 and 1.30 (2 × s, 6 H), 1.51−1.59 (m, 2 H), 1.64−1.71 (m, 2 H), 2.31 (s, 2 H), 2.49 (br s, 1 H, exchanges with D$_2$O), 3.97 and 4.00 (2 × d, AB system, J = 8.0 Hz, 2 H), 4.17 (s, 1 H), 7.12 (d, J = 8.0 Hz, 2 H), 7.28 (d, J = 8.0 Hz, 2 H). ^{13}C NMR (125 MHz) δ 7.5, 7.9, 21.2, 28.0, 29.5, 30.4, 62.1, 65.5, 67.5, 74.9, 79.2, 126.3, 128.8, 131.5, 137.4, 163.3. GC−MS (70 eV) m/z (%) 288 (2, M^+ − 29), 232 (5.9), 146 (20.4), 87 (100.0), 69 (9.3), 57 (28.9), 45 (56.8). FT-IR (film, cm^{-1}) 3383 (broad, OH), 1652 (C═N), 1462, 1304, 1010, 971, 804. Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.71; H, 8.35; N, 4.38.

(*E*)-1,2-Epoxy-1-(1-hydroxycyclohexyl)-1-(4,4-dimethyl-2-oxazolin-2-yl)-2-*p*-tolylethane (4h): overall yield 70%, conv. 68%, dr = 96:4, oil. ^{1}H NMR (500 MHz) (selected data) δ 1.20−1.26 (m, 2 H), 1.28−1.34 (m overlapping two singlets at δ 1.30 and 1.32, 2 H), 1.30 and 1.34 (2 × s, 2 × 3 H), 1.45−1.59 (m, 6 H), 2.31 (m, 3 H), 3.42 (br s, 1 H, exchanges with D$_2$O), 3.97 and 4.00 (2 × d, AB system, J = 8.2 Hz, 2 H), 4.28 (s, 1 H), 7.06−7.28 (2 m, 4 H). ^{13}C NMR (125 MHz) δ 20.9, 21.0, 21.2, 25.4, 28.07, 28.10, 33.1, 34.1, 62.70, 62.73, 65.1, 67.7, 72.1, 78.8, 126.3, 128.8, 129.2, 131.4, 137.4, 163.4. GC−MS (70 eV) m/z (%) 329 (3.5, M^+), 312 (2.2), 231 (9.2), 209 (8.8), 146 (41.9), 99 (100.0), 81 (37.9), 55 (13.2), 41 (7.5). FT-IR (film, cm^{-1}) 3376 (br, OH), 2932, 1648 (s, CN), 1517, 1448, 998, 805, 591. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 72.61; H, 8.07; N, 4.22.

(*E*)-1,2-Epoxy-1-hydroxydiphenylmethyl-1-(4,4-dimethyl-2-oxazolin-2-yl)-2-*p*-tolylethane (4i): 60%, conv. > 95%, dr > 99:1. Mp 166−168 °C (hexane). ^{1}H NMR (500 MHz) δ 0.77 (s, 3 H), 1.15 (s, 3 H), 2.18 (s, 3 H), 3.83 (d, J = 8.2 Hz, 2 H), 3.90 (d, J = 8.2 Hz, 2 H), 4.33 (s, 1 H), 6.38 (s, 1 H, exchanges with D$_2$O), 6.66−6.72 (m, 4 H), 6.83−6.90 (m, 3 H), 7.06−7.12 (m, 5 H), 7.43−7.44 (m, 2 H). ^{13}C NMR (125 MHz) δ 21.0, 27.2, 27.5, 63.6, 65.8, 67.8, 79.0, 79.1, 125.6, 126.1, 126.3, 126.6, 126.6, 127.5, 127.6, 128.0, 129.0, 135.8, 140.6, 147.0, 164.8. GC−MS (70 eV) m/z (%) 413 (44.1, M^+), 394 (18.7), 292 (58.4), 183 (99.2), 105 (100.0), 77 (39.7). FT-IR (KBr, cm^{-1}) 3322 (br, OH), 3056, 2958, 1650 (s, CN), 1450, 1315, 1180, 792, 747. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.17; H, 6.45; N, 3.27.

(*syn*)-3,4-Epoxy-3-(4,4-dimethyl-2-oxazolin-2-yl)-4-*p*-tolylbutan-2-ol (4j): overall yield 55%, see Table 2. Mp 107−109 °C (petroleum ether). ^{1}H NMR (500 MHz) δ 1.31 and 1.33 (2 × s, 6 H), 1.39 (d, J = 6.6 Hz, 3 H), 2.32 (s, 3 H), 3.29−3.35 (br m, 1 H, q at δ 3.36 after exchange with D$_2$O, J = 6.6 Hz), 3.95 and 4.01 (2 × d, AB system, J = 8.2 Hz, 2 H), 4.44 (s, 1 H), 4.49−4.51 (br d, 1 H, exchanges with D$_2$O), 7.15−7.24 (2 m, 4 H). ^{13}C NMR (125 MHz) δ 19.7, 21.2, 28.2, 28.4, 60.8, 63.3, 65.0, 68.2, 78.5, 126.6, 129.0, 130.2, 138.2, 162.1. GC−MS (70 eV) m/z (%) 275 (2.3, M^+), 231 (9.8), 260 (6.0), 146 (100.0), 132 (19.7), 105 (12.3), 91 (7.7), 77 (6.0), 45 (6.3). FT-IR (KBr, cm^{-1}) 3406 (broad, OH), 1655 (C═N), 1365, 1100, 990, 889, 816, 566. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.19; H, 7.71; N, 4.88.

(*anti*)-3,4-Epoxy-3-(4,4-dimethyl-2-oxazolin-2-yl)-4-*p*-tolylbutan-2-ol (4j): overall yield 55%, see Table 2. Mp 112−113 °C (petroleum ether). ^{1}H NMR (500 MHz) δ 1.04 (d, J = 6.7 Hz, 3 H), 1.31 and 1.33 (2 × s, 6 H), 2.33 (s, 3 H), 3.39−3.43 (br m, 1 H, q at δ 3.45 after exchange with D$_2$O, J = 6.8 Hz), 3.94 and 4.00 (2 × d, AB system, J = 8.2 Hz, 2 H), 4.43 (br d, 1 H, exchanges with D$_2$O), 4.55 (s, 1 H), 7.14−7.25 (2 m, 4 H). ^{13}C NMR (125 MHz) δ 19.6, 21.2, 28.0, 28.3, 61.1, 61.8, 68.0, 68.2, 78.4, 126.3, 129.0, 130.2, 138.0, 161.1. GC−MS (70 eV) m/z (%) 275 (3.1, M^+), 260 (8.3), 146 (100.0), 132 (18.9), 91 (11.3), 77 (6.5), 45 (8.9). FT-IR (KBr, cm^{-1}) 3225 (broad, OH), 1663 (C═N), 1306, 1151, 1116, 816. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 70.05; H, 7.87; N, 4.96.

(*syn*)-2,3-Epoxy-2-(4,4-dimethyl-2-oxazolin-2-yl)-1-phenyl-3-*p*-tolylpropan-1-ol (4k): overall yield 69%, see Table 2. Mp 130−133 °C (petroleum ether). ^{1}H NMR (500 MHz, CDCl$_3$) δ 1.08 (s, 3 H), 1.30 (s, 3 H), 2.35 (s, 3 H), 3.85 and 3.88 (2 × d, AB system, J = 8.2 Hz, 2 H), 4.30 (br s, 1 H), 4.44 (s, 1 H), 5.5−5.6 (br s, 1 H, exchanges with D$_2$O), 7.20−7.23 (m, 3 H), 7.28−7.31 (m, 2 H), 7.37−7.39 (m, 2 H), 7.48−7.50 (m, 2 H). ^{13}C NMR (125 MHz) δ 21.2, 28.0, 28.1, 61.1, 62.5, 68.2, 69.9, 78.5, 126.3, 126.6, 127.2, 127.8, 129.2, 130.0, 138.4, 141.0, 162.2. GC−MS (70 eV) m/z (%) 337 (16.2, M^+), 232 (19.7), 216 (15.8), 146 (79.4), 107 (100.0), 91 (15.7), 79 (30.6). FT-IR (KBr, cm^{-1}) 3320 (broad, OH), 1654 (C═N), 1453, 1131, 1041, 816, 702. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 75.01; H, 6.88; N, 3.97.

(*anti*)-2,3-Epoxy-2-(4,4-dimethyl-2-oxazolin-2-yl)-1-phenyl-3-*p*-tolylpropan-1-ol (4k): overall yield 69%, see Table 2. Mp 142−143 °C (petroleum ether). ^{1}H NMR (500 MHz) δ 1.08 (s, 3 H), 1.24 (s, 3 H), 2.34 (s, 3 H), 3.83 and 3.88 (2 × d, AB system, J = 8.2 Hz, 2 H), 4.54 (br d, J = 9.7 Hz, 1 H), 4.72 (s, 1 H), 5.28 (br d, J = 10.4 Hz, 1 H, exchanges with D$_2$O), 6.94−6.97 (m, 2 H), 7.11−7.17 (2 m, 5 H), 7.30−7.32 (m, 2 H). ^{13}C NMR (125 MHz) δ 21.2, 27.7, 27.8, 62.1, 62.2, 67.8, 72.4, 78.6, 126.1, 126.7, 127.2, 127.7, 129.1, 130.2, 138.4, 140.0, 161.2. GC−MS (70 eV) m/z (%) 337 (11.9, M^+), 232 (17.8), 216 (14.2), 146 (75.2), 107 (100.0), 91 (14.9), 79 (27.8). FT-IR (KBr, cm^{-1}) 3203 (broad, OH), 1653 (C═N), 1138, 1062, 940, 698. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 75.14; H, 7.00; N, 4.21.

(*Z*)-1,2-Epoxy-2-(4,4-dimethyl-2-oxazolin-2-yl)-3-ethyl-1-*p*-tolylpentan-3-ol (8a): overall yield 60%, conv. 86%, dr *Z*:*E* = 95:5, oil. ^{1}H NMR (500 MHz) (selected data) δ 1.00 (t overlapping two singlets at δ 1.01 and 1.02, J = 7.5 Hz, 3 H), 1.01 and 1.02 (2 × s, 6 H), 1.05 (t, J = 7.4 Hz, 3 H), 1.62 (q, J = 7.5 Hz, 2 H), 1.81 (qd, J = 7.4, 2.0 Hz, 2 H), 2.26 (br s overlapping s at δ 2.28, exchanges with D$_2$O, 1 H), 2.28 (s, 3 H), 3.58 (d, J = 8.0 Hz, 1 H), 3.70 (d, J = 8.0 Hz, 1 H), 4.29 (s, 1 H), 7.06−7.22 (2 m, 4 H). ^{13}C NMR (125 MHz) (selected data) δ 7.2, 8.2, 21.1, 27.7, 29.4, 31.6, 58.6, 66.3, 67.2, 73.3, 126.2, 128.5, 130.9, 137.7, 159.6. GC−MS (70 eV) m/z (%) 317 (2.44, M^+), 288 (5.69), 232 (11.90), 146 (59.79), 132 (21.07), 87 (100.0), 77 (11.92), 57 (60.73), 45 (77.76). FT-IR (film, cm^{-1}) 3423 (br, OH), 2968, 1665 (s, CN), 1518, 1462, 1365, 1106, 970, 804, 618.

Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 72.03; H, 8.79; N, 4.28.

(*Z*)-1,2-Epoxy-1-(4,4-dimethyl-2-oxazolin-2-yl)-1-(1-hydroxycyclohexyl)-2-*p*-tolylethane (8b): overall yield 71%, conv. 83%, dr *Z*:*E* = 90:10. Mp 111−112 °C (hexane). ^{1}H NMR (500 MHz) (selected data) δ 0.97 (s, 3 H), 1.07 (s, 3 H), 1.43−1.49 (m, 1 H), 1.55−1.61 (m, 2 H), 1.63−1.72 (m, 6 H), 1.82−1.87 (m, 1 H), 2.29 (s, 3 H), 2.49 (s, 1 H, exchanges with D_2O), 3.65 and 3.68 (2 × d, AB system, J = 8.2 Hz, 2 H), 4.34 (s, 1 H), 7.07−7.19 (2 m, 4 H). ^{13}C NMR (125 MHz) δ 21.2, 21.3, 25.6, 27.8, 27.9, 33.2, 33.5, 58.9, 58.9, 67.4, 67.8, 70.9, 78.8, 126.1, 128.5, 131.1, 137.7, 159.8. GC−MS (70 eV) *m*/*z* (%) 329 (5.7, M^+), 314 (1.5), 209 (11.2), 146 (41.2), 132 (17.4), 99 (100.0), 81 (33.2), 55 (10.9), 41 (6.2). FT-IR (KBr, cm^{-1}) 3320 (br, OH), 2926, 1660 (s, CN), 1354, 1103, 987, 803. Anal. Calcd for $C_{20}H_{27}NO_3$: C, 72.92; H, 8.26; N, 4.25. Found: C, 73.32; H, 8.63; N, 4.01.

(*syn* + *anti*)-3,4-Epoxy-3-(4,4-dimethyl-2-oxazolin-2-yl)-4-*p*-tolylbutan-2-ol (8c): overall yield 64%, conv. 70%, see Table 2. Mp 110−115 °C (hexane). *syn*/*anti* diastereomeric mixture refers to the *Z* epoxy alcohol. ^{1}H NMR (500 MHz) (*syn* + *anti*) δ 1.01 (s, 2 × 3 H, major + minor), 1.02 (s, 3 H, minor), 1.09 (s, 3 H, major), 1.30 (d, J = 6.0 Hz, 3 H, minor), 1.37 (d, J = 6.4 Hz, 3 H, major), 2.29 (s, 2 × 3 H, major + minor), 2.5−2.7 (br s, 2 × 1 H, exchanges with D_2O, major + minor), 3.61 and 3.73 (2 × d, AB system, J = 8.1 Hz, 2 H, major), 3.66 and 3.68 (2 × d, AB system, J = 8.1 Hz, 2 H, minor), 3.84 (br q, J = 6.3 Hz, 1 H, major), 4.18 (s, 1 H, major), 4.29 (br q, J = 6.3 Hz, 1 H, minor), 4.34 (s, 1 H, minor), 7.07−7.24 (3 m, 2 × 4 H, major + minor). ^{13}C NMR (125 MHz) (selected data) δ 18.9 (minor), 19.1 (major), 21.2, 27.88 (minor), 27.93 (minor), 28.0 (major), 59.9 (minor), 61.9 (major), 64.6 (major), 65.5 (minor), 66.5 (minor), 67.4 (minor), 67.6 (major), 69.3 (major), 78.8 (major), 79.0 (minor), 126.3 (major), 126.4 (minor), 128.5 (minor), 128.5 (major), 130.5 (major), 130.7 (minor), 137.7 (minor), 137.9 (major), 160.1 (major), 160.2 (minor). GC−MS (70 eV) (major) *m*/*z* (%) 275 (2.7, M^+), 260 (5.0), 146 (100.0), 132 (13.6), 119 (2.7), 91 (7.3), 45 (6.1). GC−MS (70 eV) (minor) *m*/*z* (%) 275 (2.0, M^+), 260 (3.4), 146 (100.0), 132 (11.7), 119 (8.5), 91 (6.4), 45 (5.7). FT-IR (KBr, cm^{-1}) (*syn* + *anti*) 3252 (broad, OH), 1666 (C═N), 1362, 1114, 1070, 807. Anal. Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.81; H, 7.74; N, 5.13.

(*syn* + *anti*)-2-(4,4-Dimethyl-2-oxazolin-2-yl)-2,3-epoxy-1-phenyl-3-*p*-tolylpropan-1-ol (8d): overall yield 95%, quantitative conv., see Table 2. Mp 146−148 °C (petroleum ether). *syn*/*anti* diastereomeric mixture refers to the *Z* epoxy alcohol. ^{1}H NMR (500 MHz) (*syn* + *anti*) δ 0.77 (s, 3 H, minor), 0.89 (s, 3 H, major), 0.92 (s, 3 H, minor), 0.95 (s, 3 H, major), 2.30 (s, 3 H, major), 2.32 (s, 3 H, minor), 3.1−3.3 (broad s, 2 H, exchanges with D_2O, major + minor), 3.42 and 3.55 (2 × d, AB system, J = 8.2 Hz, 2 H, major), 3.46 and 3.53 (2 × d, AB system, J = 8.2 Hz, 2 H, minor), 4.27 (s, 1 H, major), 4.41 (s, 1 H, minor), 4.74 (s, 1 H, major), 5.26 (s, 1 H, minor), 7.07−7.10 (m, 4 H, 2 H minor + 2 H major), 7.24−7.35 (2 m, 10 H, 5 H major + 5 H minor), 7.47−7.49 (m, 4 H, 2 H minor + 2 H major). ^{13}C NMR (125 MHz) (*syn* + *anti*) *(selected* data) δ 21.1 (major + minor), 27.5 (minor), 27.6 (major + minor), 27.8 (major), 59.5 (minor), 62.4, 62.5, 64.6, 67.2 (minor), 67.4 (major), 71.6 (minor), 75.6 (major), 78.6 (major), 78.8 (minor), 126.1 (major), 126.3 (major), 126.4 (minor), 127.3 (minor), 127.6 (minor), 128.1 (major), 128.3 (minor), 128.4 (minor), 128.5 (major), 130.3 (major), 130.6 (minor), 137.7 (minor), 137.9 (major), 139.3 (minor), 139.6 (major), 160.1 (minor), 160.2 (major). GC−MS (70 eV) (major) *m*/*z* (%) 337 (9.8, M^+), 232 (12.1), 146 (68.7), 132 (25.9), 107 (100.0), 91 (11.0), 79 (23.3). GC−MS (70 eV) (minor) *m*/*z* (%) 337 (8.0, M^+), 232 (7.6), 146 (64.0), 132 (20.7), 107 (100.0), 91 (9.7), 79 (20.8). FT-IR (KBr, cm^{-1}) (*syn* + *anti*) 3192 (broad, OH), 1662 (C═N), 1366, 1105, 1054, 745, 701. Anal. Calcd for $C_{21}H_{23}NO_3$: C, 74.75; H, 6.87; N, 4.15. Found: C, 74.53; H, 7.19; N, 3.94.

Preparation of Oxazolinyl Epoxide 12a. A solution of *N*,*N*-diisopropylethylamine (227 μL, 1.3 mmol) and dibutylboron triflate (1.3 mL, 1.3 mmol of a 1 M solution in CH_2Cl_2) in 5 mL of anhyd CH_2Cl_2 was prepared at −78 °C under N_2 and stirred for 10 min. To this milky suspension was added a solution of oxazoline **9** (240 mg, 1.0 mmol, in 4 mL of CH_2Cl_2) dropwise, and the resulting mixture was stirred at −78 °C for 1 h. After this time, a solution of 4,4′-dimethylbenzophenone (273 mg, 1.3 mmol, in 4 mL of CH_2Cl_2) was added dropwise, and the temperature was raised gradually. After 2.5 h the reaction mixture was quenched with a buffer solution (Na_2HPO_4/NaH_2PO_4, pH 7.1). MeOH and H_2O_2 were subsequently added (8 and 4 mL, respectively), and the whole mixture was poured into 30 mL of saturated brine. The organic layer was separated, and the aqueous layer extracted with AcOEt (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The residue was dissolved in *i*-PrOH (5 mL) and treated with NaOH 2 w/w (10 mL). The crude product was purified by flash chromatography (petroleum ether/AcOEt = 6:4, R_f 0.4) to give 320 mg (93% yield, conv. 83%) of (2*S*,4′*S*,5′*S*)-4-methoxymethyl-5-phenyl-2-(3,3-bis-*p*-tolyloxiranyl)-2-oxazoline (**12a**): dr = 93:7. $[\alpha]_D$ − 4.9 (c 1 $CHCl_3$). Mp 108−109 °C (hexane). ^{1}H NMR (500 MHz) δ 2.33 (s, 3 H), 2.40 (s, 3 H), 3.37 (s, 3 H), 3.45 (dd, J = 9.7, 6.2 Hz, 1 H), 3.56 (dd, J = 9.7, 4.2 Hz, 1 H), 3.96−4.00 (m, 1 H), 4.20 (s, 1 H), 5.12 (d, J = 7.4 Hz, 1 H), 6.91−6.93 (m, 2 H), 7.12−7.29 (2 m, 9 H), 7.41−7.43 (m, 2 H). ^{13}C NMR (125 MHz) δ 20.9, 21.1, 58.9, 66.4, 73.5, 73.9, 83.9, 125.6, 127.0, 127.8, 127.9, 128.3, 128.3, 128.7, 132.7, 136.0, 137.5, 137.9, 139.7, 162.0. GC−MS (70 eV) *m*/*z* (%) 413 (45.8, M^+), 278 (6.9), 222 (13.8), 195 (100.0), 165 (27.0), 45 (27.4). FT-IR (KBr, cm^{-1}) (selected data) 1673 (C═N), 1512, 1455, 1201, 1132, 973, 823, 758, 697, 593, 560. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.56; H, 6.88; N, 3.34.

Preparation of Oxazolinyl Epoxide 12b. This compound was prepared by the same procedure followed for **12a** with the exception that 9-borabicyclo[3.3.1]nonyl trifluoromethanesulfonate, 0.5 M in hexane, was used at −60 °C. The reaction was quenched as above after 1.5 h. Treatment with NaOH/*i*-PrOH afforded the crude epoxide, which was purified by flash chromatography (petroleum ether/AcOEt = 6:4, R_f 0.4) to give 310 mg (75% yield, conv. quantitative) of (2*R*,4′*S*,5′*S*)-4-methoxymethyl-5-phenyl-2-(3,3-bis-*p*-tolyloxiranyl)-2-oxazoline (**12b**): dr = 95:5. $[\alpha]_D$ −30.6 (c 1 $CHCl_3$), oil. ^{1}H NMR (500 MHz) δ 2.31 (s, 3 H), 2.39 (s, 3 H), 3.19 (dd, J = 9.7, 6.7 Hz, 1 H), 3.31 (s, 3 H), 3.45 (dd, J = 9.7, 4.7 Hz, 1 H), 3.95−4.02 (m, 1 H), 4.22 (s, 1 H), 5.19 (d, J = 7.7 Hz, 1 H), 6.70−6.72 (m, 2 H), 7.11−7.25 (3 m, 9 H), 7.41−7.43 (m, 2 H). ^{13}C NMR (125 MHz) δ 20.9, 21.2, 59.0, 59.3, 66.4, 73.7, 74.1, 84.2, 125.2, 126.6, 127.7, 127.9, 128.2, 128.7, 128.9, 132.8, 136.1, 137.6, 138.0, 139.5, 162.4. GC−MS (70 eV) *m*/*z* (%) 413 (40.5, M^+), 396 (23.9), 266 (25.1), 236 (34.0), 195 (100.0), 165 (33.8), 91 (22.7), 45 (56.3). FT-IR (film, cm^{-1}) 1659 (C═N), 1452, 979, 816, 699. Anal. Calcd for $C_{27}H_{27}NO_3$: C, 78.42; H, 6.58; N, 3.39. Found: C, 78.39; H, 6.55; N, 3.39.

(2*S*,4′*S*,5′*S*)-2-Deutero-4-methoxymethyl-5-phenyl-2-(3,3-bis-*p*-tolyloxiranyl)-2-oxazoline (12c): overall yield 75%, dr = 92:8, 100% D. Mp 108−109 °C (hexane). ^{1}H NMR (300 MHz) (selected data) δ 2.31 (s, 3 H), 2.36 (s, 3 H), 3.35 (s, 3 H), 3.41 (dd, J = 9.7, 6.2 Hz, 1 H), 3.52 (dd, J = 9.7, 4.2 Hz, 1 H), 3.91−3.97 (m, 1 H), 5.06 (d, J = 7.4 Hz, 1 H), 6.87−6.91 (m, 2 H), 7.12−7.25 (2 m, 9 H), 7.34−7.37 (m, 2 H). GC−MS (70 eV) *m*/*z* (%) 414 (33.2, M^+), 413 (32.1), 278 (6.4), 222 (17.6), 195 (100.0), 180 (27.5), 165 (28.4), 45 (40.6). FT-IR (KBr, cm^{-1}) 1668 (C═N), 1496, 1449, 1127, 758, 699. Anal. Calcd for $C_{27}H_{26}DNO_3$: C, 78.23; H, 6.81; N, 3.38. Found: C, 78.04; H, 6.66; N, 3.43.

(2*S*,4′*S*,5′*S*)-2-Methyl-4-methoxymethyl-5-phenyl-2-(3,3-bis-*p*-tolyloxiranyl)-2-oxazoline (12d): overall yield 68%, dr = 80:20, oil. ^{1}H NMR (500 MHz) (selected data for the major isomer) δ 1.51 (s, 3 H), 2.31 and 2.33 (2 × s, 2 × 3 H), 3.29−3.34 (m overlapping s at δ 3.34, 1 H), 3.34 (s, 3 H), 3.50 (dd, J = 9.8, 4.5 Hz, 1 H), 3.91−3.95 (m, 1 H), 5.02 (d, J = 7.5 Hz, 1 H), 6.81−6.83 (m, 2 H), 7.08−7.46 (3 m, 11 H).^{13}C NMR (125 MHz) (selected data for the major isomer) δ 18.6, 21.1, 21.1, 59.1, 63.7, 70.3, 73.9, 74.1, 84.3, 125.9, 127.2, 127.3, 128.1, 128.4, 128.5, 128.9, 135.1, 135.2, 137.1, 137.4, 139.9, 165.2. GC−MS (70 eV) (selected data for the major isomer) *m*/*z* (%) 427 (1.9, M^+), 410 (4.8), 356 (5.6), 280 (28.3), 236 (100.0), 210

(12.9), 179 (25.0), 91 (6.2). FTIR (film, cm^{-1}) (selected data) 1675 (s, CN), 1608, 1513, 1453, 1261,808, 733, 700. Anal. Calcd for $C_{28}H_{29}NO_3$: C, 78.66; H, 6.84; N, 3.28. Found: C, 78.45; H, 6.67; N, 3.32.

(*Z*)-1,2-Epoxy-2-(4,4-dimethyl-2-oxazolin-2-yl)-1-*p*-tolylbutane (7b): overall yield (*E* and *Z* isomers) 70%, see Scheme 3, oil. ^{1}H NMR (300 MHz) δ 1.00 (s, 3 H), 1.05 (s, 3 H), 1.08 (t, J = 7.5 Hz, 3 H), 1.67 (dq like sextet, J = 7.4 and 14.4 Hz, 1 H), 2.26 (67 (dq like sextet partially overlapping s at δ 2.29, J = 7.4 and 14.4 Hz, 1 H), 2.29 (s, 3 H), 3.65 and 3.68 (2 × d, J = 8.1 Hz, 2 H), 3.99 (s, 1 H), 7.06−7.08 (m, 2 H), 7.22−7.24 (m, 2 H). ^{13}C NMR (125 MHz) δ 8.8, 21.1, 27.5, 28.0, 28.1, 62.9, 63.7, 67.4, 79.1, 126.4, 128.4, 131.2, 137.6, 160.9. GC−MS (70 eV) *m*/*z* (%) 259 (2.5, M^+), 244 (3.7), 202 (3.4), 146 (100.0), 119 (5.5), 103 (4.2), 91 (7.3), 57 (14.9). FT-IR (film, cm^{-1}) 1671 (s, CN), 1461, 1121, 976, 810. Anal. Calcd for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16; N, 5.40. Found: C, 74.37; H, 7.38; N, 5.37.

(*E* + *Z*)-1,2-Epoxy-1-deutero-1-(4,4-dimethyl-2-oxazolin-2-yl)-2-*p*-tolylethane (4c + 7c): overall yield 75%, 100% D, dr *E*:*Z* = 17:83, oil. ^{1}H NMR (300 MHz) (selected data for the major isomer) δ 0.99 (s, 3 H), 1.10 (s, 3 H), 2.29 (s, 3 H), 3.68 and 3.72 (2 × d, AB system, J = 8.1 Hz, 2 H), 4.17 (s, 1 H), 7.06−7.09 (m, 2 H), 7.25−7.28 (m, 2 H). GC−MS (70 eV) (selected data for the major isomer) *m*/*z* (%) 232 (3.7, M^+), 217 (9.5), 177 (13.8), 146 (100.0), 121 (10.7), 91 (13.8), 41 (17.1). FT-IR (film, cm^{-1}) (selected data) 1655 (s, CN). Anal. Calcd for $C_{14}H_{16}DNO_2$: C, 72.39; H, 7.81; N, 6.03. Found: C, 72.02; H, 7.52; N, 6.15.

(*E*)-1,2-Bis(4,4-dimethyl-2-oxazolin-2-yl)ethene (6): mp 105−106 °C (Et_2O/hexane). ^{1}H NMR (500 MHz) δ 1.22 (s, 12 H), 3.91 (s, 4 H), 6.66 (s, 2 H). ^{13}C NMR (125 MHz) δ 28.0, 67.6, 78.8, 126.4, 160.4. GC−MS (70 eV) *m*/*z* (%) 222 (6.2, M^+), 207 (100.0), 134 (14.5), 41 (20.3). FT-IR (KBr, cm^{-1}) 3044, 1633 (C═N), 1455, 1355, 1294, 1194, 1016, 988, 922. Anal. Calcd for $C_{12}H_{18}N_2O_2$: C, 64.84; H, 8.16; N, 12.60. Found: C, 64.63; H, 8.13; N, 12.28.

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Supporting Information Available: Copies of spectra (^{1}H or ^{13}C NMR) for compounds **4a**−**k**, **8a**−**d**, **12b**−**d**, **7b**, **4a** + **7a**, **4c** + **7c**. ORTEP view of compound **12a** (Figure S1). Geometry tables and crystallographic data for compound **12a**. Table of Cartesian coordinates of HF/6-31+G* optimized structures (*trans*-**3a′** and *cis*-**3b′**). This material is available free of charge via the Internet at http://pubs.acs.org.

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