Azaenolates of 2-Chloromethyl-4-methoxymethyl-5-phenyl-2-oxazoline − A Highly Diastereo- and Enantioselective Synthesis of Oxazolinyloxiranes

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The oxazoline-derived titanium azaenolate **6** couples highly stereoselectively with aldehydes affording highly optically pure oxazolinyloxiranes **7**. The epoxide **7a** has been deblocked to form the optically pure formyl oxirane **9**. In contrast, the corresponding boron azaenolates **2** and **3** couple with very poor or no stereoselectivity. Lithium, aluminum and tin azaenolates have also been shortly studied.

Oxazoline-derived azaenolates have been proved to be useful intermediates in synthetic organic chemistry.[1] While those derived from alkyloxazolines have been extensively investigated, azaenolates of α-heterosubstituted oxazolines (Figure 1), which are equally useful from the synthetic standpoint, have not been studied with the same thoroughness and interest, despite the fact that the α-Y group is expected to dictate the geometry, *E* or *Z*, of the azaenolate, and consequently the stereochemistry of the reactions with electrophiles.[2,3]

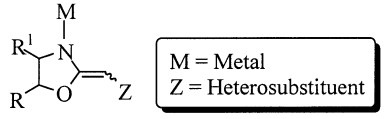
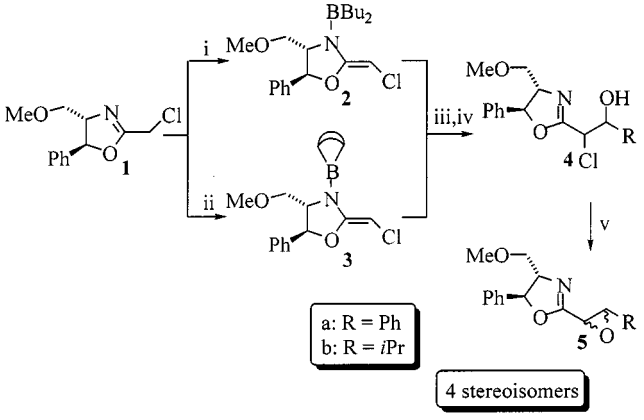


Figure 1. Heterosubstituted azaenolates

Lithiated α-amino-[4] and α-alkoxy-substituted[5] oxazolines have been studied in some detail; however, we felt that metallated α-haloalkyloxazolines, which have already received some attention,[6] deserved a much deeper examination. Lithiated chloroalkyloxazolines, some of which have also been investigated spectroscopically,[7] have been shown to behave as Darzens reagents and couple with carbonyl compounds and imines to give oxazolinyloxiranes and aziridines.[8] However, the reactions of lithiated chiral oxazolines have been found to occur with poor diastereoselectivity no matter what the electrophile and the experimental conditions.[6a,9] In contrast, the corresponding boron[10] and titanium[11] azaenolates react with ketones with excellent diastereoselectivity affording highly optically pure oxazolinyl and then formyl oxiranes by the elaboration of the oxazolinyl ring.

Here we report on the coupling reaction of azaenolates of (4*S*,5*S*)-2-chloromethyl-4-methoxymethyl-5-phenyl-2-oxazoline (**1**) with aldehydes (Scheme 1). The main purpose was the development of a simple procedure to synthesize stereodefined oxazolinyloxiranes suitable for elaboration to more substituted, optically pure formyl oxiranes and their derivatives.



Reagents: (i) Bu_2BOTf, iPr_2NEt; (ii) 9-BBNOTf, iPr_2NEt; (iii) RCHO; (iv) H^+; (v) NaOH/*i*PrOH;

Scheme 1. Reaction of **1**, via the boron azaenolates **2** and **3**, with aldehydes to give a mixture of four stereoisomeric chlorohydrins **4** and the corresponding epoxides **5**

Treatment of oxazoline **1** with iPr_2NEt and Bu_2BOTf in CH_2Cl_2 at 0 °C provided the boron azaenolate **2**, which was then reacted with benzaldehyde to produce a mixture of four stereoisomeric chlorohydrins **4** in a 28:6:42:24 ratio (Scheme 1). These chlorohydrins were then converted quantitatively into the oxiranes **5a** upon treatment with NaOH in *i*PrOH (stereoisomeric ratio: 28:6:42:24). Exactly the same result was obtained when the reaction was carried out at −80 °C. Similarly, the reaction of boron azaenolate **3**, prepared from **1** and 9-BBNOTf/iPr_2NEt in Et_2O at 0 °C, with PhCHO proceeded with poor diastereoselectivity affording a diastereomeric mixture of the oxiranes **5a** (stereoisomeric ratio: 24:26:25:25). Equally poorly diastereoselective was the reaction of boron azaenolate **2** (CH_2Cl_2, 0 °C) with *i*PrCHO that ended up with the formation of a diastereomeric mixture of oxiranes **5b** (stereoisomeric ratio: 12:5:66:17). This sounds rather surprising in view of the fact

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that azaenolates **2** and **3** have been found to couple highly diastereoselectively with ketones. Comparable results were obtained when the lithiated oxazoline **1** (LDA, THF, −80 °C) was treated with PhCHO to give the mixture of oxiranes **5a** with a reasonable diastereoselectivity (*trans*/*cis* ratio = 85:15) but with no enantioselection at all (*dr* =50:50 in both the diastereomers).

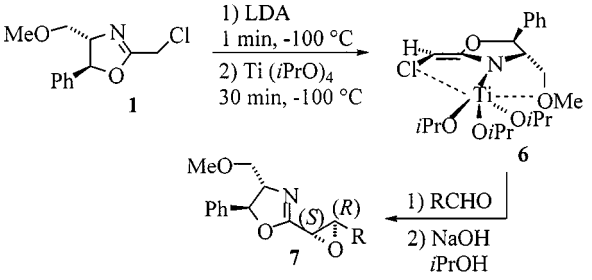
Completely different results were obtained when the titanium azaenolate of **1** was used (Table 1). Oxazoline **1** (Scheme 2) was first lithiated with LDA at −100 °C in THF and then added to Ti(O*i*Pr)$_4$. The putative titanium enolate **6** was then reacted with PhCHO to produce oxazolinyloxirane **7a** (*trans*/*cis* ratio > 95:5; Scheme 2, Table 1) highly stereoselectively. The *trans* isomer, which was further purified by chromatography and assigned its configuration on the basis of ^{1}H NMR spectroscopic data ($^3J_{H\text{-}H}$ = 1.9 Hz), was optically pure (dr_{trans} > 95%, by GC and ^{1}H NMR, $[\alpha]_D^{24}$ = +219 [*c* = 1, $CHCl_3$]). The newly created stereocenters were assigned the 1*S*,2*R* configuration by comparison of the formyl oxirane **9**, obtained by deblocking (methylation-reduction-hydrolysis according to a known protocol[8a]) of the oxazolinyl ring of **7a** ($[\alpha]_D^{24}$ = −12.6 [*c* = 1 $CHCl_3$]), with a specimen prepared from the commercially available epoxy alcohol **8**, with the 2*R*,3*R* configuration,[12] by Swern oxidation ($[\alpha]_D^{24}$ = −12.8 [*c* = 1 $CHCl_3$]) (see typical procedure and Scheme 3).[13] This represents a convenient route to stereodefined formyl oxiranes with two stereocenters on the oxirane ring and adds to the reported synthetic procedure based on the Sharpless oxidation of allylic alcohols. Comparable results were obtained when the titanium azaenolate **6** was treated with other aromatic aldehydes. The *trans* oxazolinyloxiranes formed in good yield and excellent diastereoselectivity (Table 1). Moreover, equally highly stereoselective was the coupling of **6** with aliphatic enolizable aldehydes.

Table 1. Synthesis of oxazolinyl oxiranes **7a**−**f**

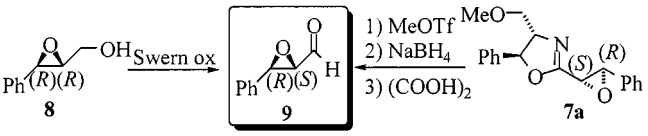
R	Yield [%][a],[b]	$dr_{trans/cis}$ [c]	Configuration	$[\alpha]_D^{24}$ (*c* = 1, $CHCl_3$)
7a Ph	70	>95:5	1*S*,2*R*	+219
7b *p*-Br-Ph	60	95:5	1*S*,2*R*[d]	+90.4
7c *p*-NO_2-Ph	50	95:5	1*S*,2*R*[d]	+156
7d $(CH_3)_2CH$	75	88:12	1*S*,2*R*[d]	−21.1
7e $CH_3(CH_2)_6$	60	90:10	1*S*,2*R*[d]	+0.5
7f $CH_3(CH_2)_7$	60	90:10	1*S*,2*R*[d]	−1.4

[a] Isolated yields. − [b] All new oxazolinyloxiranes **7** showed satisfactory ^{1}H, ^{13}C NMR, MS and IR spectroscopic data. − [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy and GC. The diastereomeric ratio for each *trans* isomer was >95%. − [d] Presumed configuration.

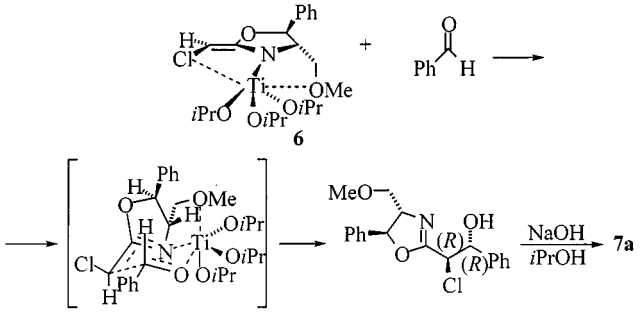
A plausible explanation for the observed stereoselectivity relies on the assumption that the stereoselective-determining step is the azaenolate formation,[14] the *E* configured titanium azaenolate is the more stable isomer[15] and there is no *Z* ⇄ *E* interconversion.[3−5] The 1*R*,2*R* configuration of the intermediate chlorohydrin, which would lead stereospecifically to the 1*S*,2*R* oxazolinyloxirane, can be explained by assuming that the aldehyde attacks the titanium azaenolate according to an unlike (*re*,*si*) topicity from below via a Zimmerman−Traxler-type six-membered chair-like transition state which places the phenyl and chlorine substituents both pseudo-equatorial (Scheme 4).



Scheme 2. Reaction of **1**, via the titanium azaenolate **6**, with aldehydes to give the oxazolinyloxiranes **7**

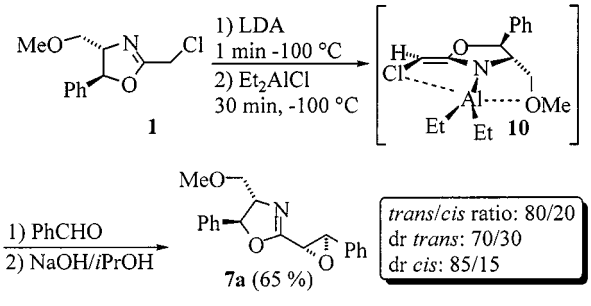


Scheme 3. Synthesis of optically active formyl oxirane **9** from epoxyalcohol **8** and deblocking of the oxazolinyl ring of **7a**



Scheme 4. Reaction of PhCHO with the *E* configured titanium azaenolate **6** via a favored Zimmerman−Traxler-type transition state

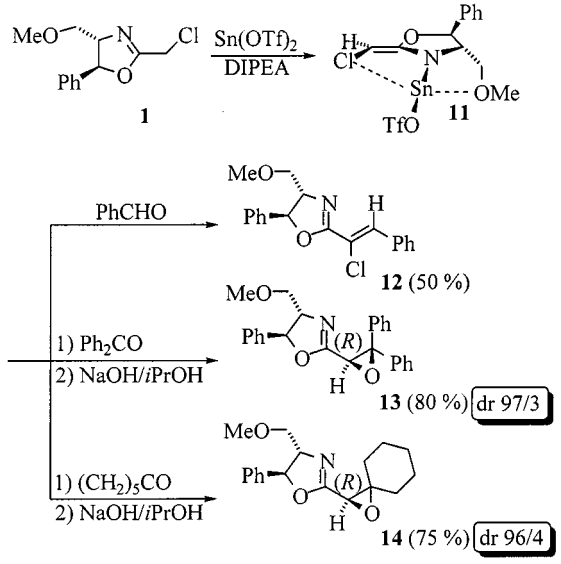
The coupling reactions of aluminum and tin azaenolates of oxazoline **1** have also been briefly investigated (Scheme 5). Oxazoline **1** was first lithiated with LDA at



Scheme 5. Reaction of **1**, via the aluminum azaenolate **10**, with PhCHO to give **7a**

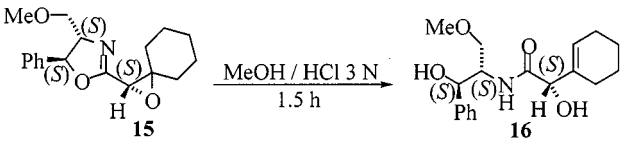
−100 °C in THF and then added to Et_2AlCl. The resulting azaenolate **10** (not isolated) was then reacted with PhCHO to produce, in a moderately stereoselective manner, the oxazolinyloxirane **7a** (overall yield: 65%, mixture of diastereoisomers separable by column chromatography on silica gel: hexane/AcOEt, 75:25; *trans*/*cis* ratio = 80:20; dr_{trans} = 70:30; dr_{cis} = 85:15).

In contrast, the reaction of the tin azaenolate **11** (Scheme 6), generated upon treatment of oxazoline **1** with $Sn(OTf)_2$ and diisopropylethylamine (DIPEA) in THF at room temperature, with PhCHO furnished the *Z*-chloro-(oxazolinyl)styrene **12** (50% yield),[16] while the reaction of **11** with benzophenone and cyclohexanone led to the oxazolinyloxiranes **13** and **14**, respectively, with excellent stereoselectivity (80%, *dr* = 97:3; 75%, *dr* = 96:4).



Scheme 6. Reaction of **1**, via the tin azaenolate **11**, with PhCHO, Ph_2CO and cyclohexanone to give the oxazolinylstyrene **12** and oxazolinyl epoxides **13** and **14**

The absolute configuration of the new stereocenter of oxirane **13** was assigned by comparison with a specimen prepared as reported previously.[11] The *R* configuration of the oxirane **14**, on the other hand, was established by comparison with its *S* stereoisomer **15**,[11] whose structure was determined by an X-ray analysis carried out on the α-hydroxyamide **16**, which in turn was obtained by deblocking of both the heterocyclic rings of **15** (Scheme 7).



Scheme 7. Synthesis of the hydroxyamide **16** from the oxazolinyl epoxide **15**

In conclusion, this paper illustrates that, among the azaenolates of a chiral oxazoline such as **1**, the most useful procedure for the preparation of highly optically pure oxazolinyloxiranes is the one that uses titanium. The specificity of the role of the titanium azaenolate is evidenced by comparison with the corresponding lithium, boron, aluminum and tin derivatives, which react with poor stereoselectivity. More work is under way to provide a rationalization of the experimentally observed titanium stereoselectivity.

Experimental Section

General: Tetrahydrofuran (THF) was freshly distilled under a nitrogen atmosphere over sodium benzophenone ketyl. Diisopropylamine was distilled over finely powdered calcium hydride. $Ti(iPrO)_4$ was distillated prior to use while all the other chemicals were of commercial grade (Aldrich) and used without further purification. Petroleum ether refers to the 40−60 °C boiling fraction. A commercial solution of *n*BuLi (in hexanes) from Aldrich was titrated with *N*-pivaloyl-*o*-toluidine prior to use.[17] − NMR: Bruker (500 MHz and 50.3 or 125 MHz, for ^1H and ^{13}C, respectively); ^1H NMR: $CDCl_3$ as solvent (δ_H = 7.24); ^{13}C NMR: $CDCl_3$ as solvent (δ_C = 77.0). − FT-IR: Perkin−Elmer Spectrum One. − GC-MS spectrometry analyses were performed on a gas chromatograph HP 6890 (HP-5MS 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 with silica gel (70−230 mesh) and petroleum ether (or hexane)/Et_2O (or AcOEt) mixtures as the eluent. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe and septum cap technique.

Typical Procedure for the Synthesis of 7a and 9: A solution of **1** (120 mg, 0.50 mmol) in 3 mL of THF was added dropwise to a solution of LDA [0.55 mmol; from 0.55 mmol of *n*BuLi (2.4 M, 230 μL) and 0.55 mmol of iPr_2NH (80 μL)] in 6 mL of THF precooled to −98 °C under N_2. To the resulting red mixture, a solution of $Ti(iPrO)_4$ (0.70 mmol, 210 μL) in 1 mL of THF was added directly after 1 min. The mixture was stirred at −98 °C for 15 min. and a solution of PhCHO (0.65 mmol, 66 μL) in 1 mL of THF was then added. The mixture was allowed to warm to room temperature and quenched with sat. aq. NH_4Cl. The organic layer was separated and the aqueous layer filtered and extracted with AcOEt (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The crude chlorohydrin thus obtained was dissolved in *i*PrOH (5 mL) and reacted with NaOH 2% w/w (10 mL). After conversion into the epoxide (monitored by TLC) the crude product was purified by flash chromatography (petroleum ether/AcOEt, 7:3; R_f = 0.4) to give (1*S*,2*R*,4′*S*,5′*S*)-*trans*-1,2-epoxy-1-(4-methoxymethyl-5-phenyl-2-oxazolin-2-yl)-2-phenylethane (**7a**) (108 mg, 70% yield).

Oil, $dr_{trans/cis} > 95:5$, $dr_{trans} > 95\%$. − $[\alpha]_D^{24} = +219$ (c = 1, $CHCl_3$). − ^1H NMR (500 MHz): δ = 3.41 (s, 3 H, CH_3O), 3.55 (dd, J = 6.1, 9.7 Hz, 1 H, CH_aH$_b$OMe), 3.63 (dd, J = 4.4, 9.7 Hz, 1 H, CH$_a$$H_b$OMe), 3.75 (d, J = 1.9 Hz, 1 H, CH oxirane), 4.20−4.23 (m, 1 H, CHCH$_2$), 4.30 (d, J = 1.9 Hz, 1 H, CH oxirane), 5.43 (d, J = 6.8 Hz, 1 H, CHPh), 7.30−7.38 (m, 5 H, ArH). − ^{13}C NMR (50.3 MHz, APT): δ = 54.7 (CH_3O), 57.9 (*C*H), 59.3 (*C*H), 73.7 (CH_2), 74.7 (*C*H), 83.9 (*C*H), 125.4 (Ar*C*H), 125.8 (Ar*C*H), 128.3 (Ar*C*H), 128.6 (Ar*C*H), 128.8 (Ar*C*H), 135.2 (Ar*C*), 135.9 (Ar*C*), 140.0 (*C*=N). − GC-MS (70 eV): *m*/*z* (%) = 309 (0.8) [M^+], 148 (100.0), 116 (32.7), 91 (61.1), 45 (95.0). − FT-IR (film): $\tilde{\nu}$ = 1667 cm^{-1} (s, C=N).

MeOTf (0.65 mmol, 73 μL) was added to a solution of **7a** (100 mg, 0.32 mmol) in 4 mL of CH_2Cl_2 at 0 °C under N_2. The resulting mixture was stirred for 45 min., cooled to −78 °C and reacted with $NaBH_4$ (8 mg, 0.8 mmol) in EtOH/THF(1 + 4 mL, respectively). After 10 min. the reaction was quenched with sat. aq. NH_4Cl and extracted with Et_2O (3 × 20 mL). The crude mixture was purified by flash chromatography (petroleum ether/AcOEt, 7:3) and finally hydrolyzed with a solution of $(COOH)_2$ (20 mg, 0.22 mmol) in H_2O/THF (1 + 4 mL, respectively) at 0 °C. After 45 min. brine was added and the mixture extracted with Et_2O (3 × 20 mL). Evaporation of the solvent left a residue that was purified by flash chromatography (hexane/Et_2O 6:4) to give (2*S*,3*R*)-*trans*-2,3-epoxy-3-phenylpropanal **(9)** (16.5 mg, 35% overall yield).
Oil, *ee* > 95% by chiral GC analysis (β-DEX 120, Supelco, Det.: FID, 300 °C. Column head pressure: 22 psi. Oven: 110 °C. t_R = 32.96 min.). − $[\alpha]_D^{24}$ = −12.6 (*c* = 1, $CHCl_3$). − ^{1}H NMR (500 MHz): δ = 3.42 (dd, *J* = 1.7, 6.0 Hz, 1 H, C*H*CHO), 4.15 (d, *J* = 1.7 Hz, 1 H, C*H*Ph), 7.26−743 (2 m, 5 H, Ar*H*), 9.17 (d, *J* = 6.0 Hz, 1 H, C*H*O). − ^{13}C NMR (125 MHz): δ = 56.6 (*C*H oxirane), 62.9 (*C*H oxirane), 125.7 (Ar*C*H), 128.7 (Ar*C*H), 129.1 (Ar*C*H), 134.1 (Ar*C*), 196.8 (*C*HO). − GC-MS (70 eV): *m*/*z* (%) = 148 (12.6) [M^+], 147 (20.1), 119 (24.6), 105 (10.5), 91 (100.0), 77 (16.5). − FT-IR (film): $\tilde{\nu}$ = 1725 cm^{-1} (s, CO).

Oxazolinyl epoxides **7b−f, 13−14** and oxazolinylethene **12** showed the following data:

(1*S*,2*R*,4′*S*,5′*S*)-*trans*-1,2-Epoxy-1-(4-methoxymethyl-5-phenyl-2-oxazolin-2-yl)-2-*p*-bromophenylethane (7b): 60% yield. Oil, $dr_{trans/cis}$ = 95:5, dr_{trans} > 95%. − $[\alpha]_D^{24}$ = +90.4 (*c* = 1, $CHCl_3$). − ^{1}H NMR (200 MHz; selected data): δ = 3.41 (s, 3 H, CH_3O), 3.52−3.66 (m, 2 H, CH_2OCH$_3$), 3.70 (d, *J* = 1.8 Hz, 1 H, C*H* oxirane), 4.17−4.24 (m, 1 H, C*H*CH$_2$), 4.25 (d, *J* = 1.8 Hz, 1 H, C*H* oxirane), 5.42 (d, *J* = 7.0 Hz, 1 H, C*H*Ph), 7.15−7.60 (3 m, 9 H, Ar*H*). − ^{13}C NMR (50.3 MHz; selected data): δ = 54.7, 57.3, 59.3, 73.6, 74.6, 83.9, 122.8, 125.4, 127.4, 128.4, 128.8, 131.8, 139.8, 140.8, 163.1. − GC-MS (70 eV): *m*/*z* (%) = 389 (0.5) [M^+ + 2], 387 (0.5) [M^+], 342 (4.8), 148 (100.0), 116 (25.9), 89 (15.4), 67 (17.5). − FT-IR (film): $\tilde{\nu}$ = 1667 cm^{-1} (s, C=N).

(1*S*,2*R*,4′*S*,5′*S*)-*trans*-1,2-Epoxy-1-(4-methoxymethyl-5-phenyl-2-oxazolin-2-yl)-2-*p*-nitrophenylethane (7c): 50% yield. Oil, $dr_{trans/cis}$ = 95:5, dr_{trans} > 95%. − $[\alpha]_D^{24}$ = +156 (*c* = 1, $CHCl_3$). − ^{1}H NMR (200 MHz; selected data): δ = 3.40 (s, 3 H, CH_3O), 3.50−3.65 (m, 2 H, CH_2OCH$_3$), 3.70 (d, *J* = 2.4 Hz, 1 H, C*H* oxirane), 4.10−4.25 (m, 1 H, C*H*CH$_2$), 4.37 (d, *J* = 2.4 Hz, 1 H, C*H* oxirane), 5.40 (d, *J* = 8.2 Hz, 1 H, C*H*Ph), 7.20−7.50 (2 m, 7 H, Ar*H*), 8.05−8.25 (m, 2 H, Ar*H*). − ^{13}C NMR (50.3 MHz; selected data): δ = 55.1, 56.7, 59.3, 73.4, 73.7, 74.7, 84.0, 123.9, 125.4, 126.6, 128.5, 128.9, 139.6, 142.6, 148.2, 162.6. − GC-MS (70 eV): *m*/*z* (%) = 354 (0.9) [M^+], 309 (74.8), 253 (37.4), 146 (68.3), 118 (41.1), 91 (54.9), 67 (100.0). − FT-IR (film): $\tilde{\nu}$ = 1667 cm^{-1} (s, C=N).

(1*S*,2*R*,4′*S*,5′*S*)-*trans*-1,2-Epoxy-1-(4-methoxymethyl-5-phenyl-2-oxazolin-2-yl)-3-methylbutane (7d): 75% yield. Oil, $dr_{trans/cis}$ = 88:12, dr_{trans} > 95%. − $[\alpha]_D^{24}$ = −21.1 (*c* = 1, $CHCl_3$). − ^{1}H NMR (200 MHz; selected data): δ = 0.98 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.00 (d, *J* = 6.6 Hz, 3 H, CH_3), 1.64 [octet, *J* = 6.7 Hz, 1 H, C*H*(CH$_3$)$_2$], 3.15 (dd, *J* = 1.9, 6.4 Hz, 1 H, C*H* oxirane), 3.37 (s, 3 H, CH_3O), 3.46 (d, *J* = 1.9 Hz, 1 H, C*H* oxirane), 3.48 (dd, J = 6.2, 9.7 Hz, 1 H, CH_aOCH$_3$), 3.58 (dd, *J* = 4.5, 9.7 Hz, 1 H, CH_bOCH$_3$), 4.10−4.16 (m, 1 H, C*H*CH$_2$), 5.31 (d, *J* = 6.9 Hz, 1 H, C*H*Ph), 7.21−7.34 (m, 5 H, Ar*H*). − ^{13}C NMR (50.3 MHz; selected data): δ = 18.2, 18.5, 30.0, 49.9, 59.3, 63.2, 73.8, 74.5, 83.8, 125.3, 128.2, 128.7, 140.0, 164.5. − GC-MS (70 eV): *m*/*z* (%) = 230 (3.0) [M^+ − 45], 146 (2.6), 126 (100.0), 119 (3.8), 91 (4.3), 67 (4.8). − FT-IR (film): $\tilde{\nu}$ = 1666 cm^{-1} (s, C=N).

(1*S*,2*R*,4′*S*,5′*S*)-*trans*-1,2-Epoxy-1-(4-methoxymethyl-5-phenyl-2-oxazolin-2-yl)nonane (7e): 60% yield. Oil, $dr_{trans/cis}$ = 90:10, dr_{trans} > 95%. − $[\alpha]_D^{24}$ = +0.5 (*c* = 1, $CHCl_3$). − ^{1}H NMR (500 MHz; selected data): δ = 0.84 (t, *J* = 6.8 Hz, 3 H, CH_3), 1.20−1.75 [3 m, 12 H, (CH_2)$_6$], 3.28−3.35 (m, 1 H, C*H* oxirane), 3.37 (s, 3 H, CH_3O), 3.40 (d, *J* = 2.0 Hz, 1 H, C*H* oxirane), 3.49 (dd, *J* = 6.3, 9.8 Hz, 1 H, CH_aOCH$_3$), 3.58 (dd, *J* = 4.4, 9.8 Hz, 1 H, CH_bOCH$_3$), 4.11−4.14 (m, 1 H, C*H*CH$_2$), 5.32 (d, *J* = 6.9 Hz, 1 H, C*H*Ph), 7.19−7.35 (2 m, 5 H, Ar*H*). − ^{13}C NMR (125 MHz; selected data): δ = 13.7, 22.3, 25.4, 28.8, 28.9, 31.2, 31.4, 50.6, 58.0, 58.9, 73.5, 74.2, 83.5, 125.0, 127.9, 128.4, 139.8, 164.2. − GC-MS (70 eV): *m*/*z* (%) = 331 (2.2) [M^+], 286 (100.0), 230 (35.3), 196 (17.3), 146 (32.4), 126 (71.5), 91 (36.7), 67 (39.1). − FT-IR (film): $\tilde{\nu}$ = 1666 cm^{-1} (s, C=N).

(1*S*,2*R*,4′*S*,5′*S*)-*trans*-1,2-Epoxy-1-(4-methoxymethyl-5-phenyl-2-oxazolin-2-yl)decane (7f): 60% yield. Oil, $dr_{trans/cis}$ = 90:10, dr_{trans} > 95%. − $[\alpha]_D^{24}$ = −1.4 (*c* = 1, $CHCl_3$). − ^{1}H NMR (500 MHz; selected data): δ = 0.85 (t, *J* = 6.7 Hz, 3 H, CH_3), 1.20−1.75 [3 m, 14 H, (CH_2)$_7$], 3.30−3.34 (m, 1 H, C*H* oxirane), 3.38 (s, 3 H, CH_3O), 3.41 (d, *J* = 2.0 Hz, 1 H, C*H* oxirane), 3.50 (dd, *J* = 6.3, 9.7 Hz, 1 H, CH_aOCH$_3$), 3.59 (dd, *J* = 4.4, 9.7 Hz, 1 H, CH_bOCH$_3$), 4.10−4.18 (m, 1 H, C*H*CH$_2$), 5.32 (d, *J* = 6.9 Hz, 1 H, C*H*Ph), 7.21−7.36 (2 m, 5 H, Ar*H*). − ^{13}C NMR (125 MHz; selected data): δ = 14.0, 22.6, 25.7, 29.1, 29.2, 29.4, 31.4, 31.7, 50.9, 58.3, 59.2, 73.8, 74.5, 83.7, 125.3, 125.9, 128.2, 128.7, 140.1, 164.4. − GC-MS (70 eV): *m*/*z* (%) = 345 (2.2) [M^+], 300 (100.0), 244 (32.9), 194 (17.6), 146 (31.6), 126 (64.8), 91 (33.7), 67 (36.5). − FT-IR (film): $\tilde{\nu}$ = 1667 cm^{-1} (s, C=N).

(2*R*,4′*S*,5′*S*)-2-[3,3-Bis(phenyloxiranyl)]-4-methoxymethyl-5-phenyl-2-oxazoline (13): 80% yield. Oil, *dr* = 97:3. − $[\alpha]_D^{24}$ = −31.0 (*c* = 1, $CHCl_3$). − ^{1}H NMR (500 MHz; selected data): δ = 3.13 (dd, *J* = 6.8, 9.7 Hz, 1 H, CH_aOCH$_3$), 3.28 (s, 3 H, CH_3O), 3.40 (dd, *J* = 4.7, 9.7 Hz, 1 H, CH_bOCH$_3$), 4.01−4.18 (m, 1 H, C*H*CH$_2$), 4.22 (s, 1 H, C*H* oxirane), 5.17 (d, *J* = 7.7 Hz, 1 H, C*H*Ph), 6.70−6.72 (m, 2 H, Ar*H*), 7.15−7.37 (3 m, 11 H), 7.50−7.55 (m, 2 H, Ar*H*). − ^{13}C NMR (125 MHz; selected data): δ = 59.0, 59.4, 66.6, 73.7, 74.1, 84.3, 125.2, 126.7, 127.8, 128.0, 128.11, 128.15, 128.2, 128.28, 128.35, 128.4, 135.6, 138.8, 139.5, 162.2. − GC-MS (70 eV): *m*/*z* (%) = 385 (5.8) [M^+], 368 (9.9), 238 (34.6), 208 (35.9), 165 (81.4), 148 (99.6), 147 (100.0), 105 (44.3), 77 (31.7), 45 (64.9). − FT-IR (film): $\tilde{\nu}$ = 1660 cm^{-1} (s, C=N).

(2*R*,4′*S*,5′*S*)-2-(4-Methoxymethyl-5-phenyl-2-oxazolin-2-yl)-1-oxaspiro[2,5]octane (14): 75% yield. Oil, *dr* = 96:4. − $[\alpha]_D^{24}$ = −64.0 (*c* = 1, $CHCl_3$). − ^{1}H NMR (500 MHz; selected data): δ = 1.40−1.80 (2 m, 10 H, cyclohexyl), 3.36 (s, 3 H, CH_3O), 3.47 (s, 1 H, C*H* oxirane), 3.50 (dd, *J* = 6.9, 10.0 Hz, 1 H, CH_aOCH$_3$), 3.61 (dd, *J* = 5.2, 10.0 Hz, 1 H, CH_bOCH$_3$), 4.10−4.18 (m, 1 H, C*H*CH$_2$), 5.35 (d, *J* = 6.8 Hz, 1 H, C*H*Ph), 7.20−7.40 (2 m, 5 H, Ar*H*). − ^{13}C NMR (125 MHz; selected data): δ = 24.9, 25.1, 25.4, 28.9, 35.0, 56.9, 59.3, 65.5, 73.9, 84.3, 125.8, 128.5, 128.8, 140.3, 163.6. − GC-MS (70 eV): *m*/*z* (%) = 353 (2.9) [M^+], 336 (65.7), 308 (2.2), 252 (24.9), 206 (55.8), 148 (100.0), 16 (45.1), 105 (28.8), 91 (62.0), 45 (56.3). − FT-IR (film): $\tilde{\nu}$ = 1660 cm^{-1} (s, C=N).

(4*S*,5*S*)-1-Chloro-1-(4-methoxymethyl-5-phenyl-2-oxazolin-2-yl)-2-phenylethene (12): 50% yield. M.p. 69 °C − $[\alpha]_D^{24}$ = +84.5 (*c* = 1, $CHCl_3$). − ^{1}H NMR (300 MHz; selected data): δ = 3.44 (s, 3 H, CH_3O), 3.65 (dd, *J* = 6.3, 9.8 Hz, 1 H, CH_aOCH$_3$), 3.74 (dd, *J* = 4.1, 9.8 Hz, 1 H, CH_bOCH$_3$), 4.32−4.36 (m, 1 H, C*H*CH$_2$), 5.56 (d, *J* = 7.1 Hz, 1 H, C*H*Ph), 7.30−7.47 (m, 8 H, Ar*H*), 7.71 (s, 1

H, C*H*=C), 7.08−7.60. − ^{13}C NMR (75 MHz; selected data): δ = 56.9, 74.0, 75.3, 85.3, 119.1, 125.9, 128.7, 128.7, 129.1, 130.0, 130.6, 133.5, 124.8, 140.5, 162.4. − GC-MS (70 eV): *m*/*z* (%) = 327 (2.9) [M$^+$], 282 (100.0), 182 (14.7), 154 (23.8), 119 (75.3), 91 (80.7), 77 (17.4), 45 (56.3). − FT-IR (film): $\tilde{\nu}$ = 1636 cm^{-1} (s, C=N), 1607 (C=C). − $C_{19}H_{18}ClNO_2$ (327.80): calcd. C 69.62, H 5.53, N 4.27; found C 69.86, H 5.74, N 4.29.

Synthesis of (2*S*,1′*S*,2′*S*)-(+)-2-(Cyclohexen-1-yl)-2-hydroxy-*N*-(2-hydroxy-1-methoxymethyl-2-phenylethyl)acetamide (16): To a solution of oxazolinyl epoxide **15** (408 mg, 1.35 mmol) in 10 mL of MeOH, was added 3 N HCl (3 mL) and the resulting mixture refluxed for 1.5 h. The mixture was then cooled to room temp., treated with a satd. solution of $NaHCO_3$ (pH = 7) and finally extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (silica gel; CH_2Cl_2/AcOEt, 7:3) to give **16** (366 mg, 85%). M.p. 107−108 °C (CH_2Cl_2/hexane) − $[\alpha]_D^{24}$ = +74.2 (*c* = 1, $CHCl_3$). − ^{1}H NMR (500 MHz): δ = 1.18−2.0 (5 m, 8 H, cyclohexyl), 3.36 (s, 3 H, C*H*$_3$O), 3.46−3.48 (m, 1 H, exchanges with D_2O, O*H*), 3.55−3.61 (m, 2 H, C*H*$_2$OCH$_3$), 3.63−3.68 (br s, 1 H, exchanges with D_2O, O*H*), 4.20−4.23 (m, 1 H, C*H*CH$_2$), 4.31 (d, *J* = 2.7 Hz, 1 H, C*H*OH), 5.04 (d, *J* = 3.1 Hz, 1 H, C*H*Ph), 5.78−5.80 (m, 1 H, C*H*=C), 6.58 (br d, *J* = 8.1 Hz, 1 H, exchanges slowly with D_2O, N*H*), 7.23−7.32 (2 m, 5 H, Ar*H*). − ^{13}C NMR (125 MHz): δ = 21.9, 22.1, 22.2, 25.1, 54.6, 59.3, 76.7, 77.0, 77.2, 127.6, 128.3, 128.5, 136.4, 140.7, 172.9. − GC-MS (70 eV): *m*/*z* (%) = 319 (7.0) [M$^+$], 301 (7.0), 212 (30.0), 181 (100.0), 164 (32.8), 111 (97.3), 74 (80.1). − FT-IR (film): $\tilde{\nu}$ = 3416 cm^{-1}, 3152, 1637 (s, C=O), 1529. − $C_{18}H_{25}NO_4$ (319.40): calcd. C 67.69, H 7.89, N 4.39; found C 68.07, H 8.26, N 4.44.

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