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On the coupling reaction of lithium azaenolates of chiral oxazolines with carbonyl compounds

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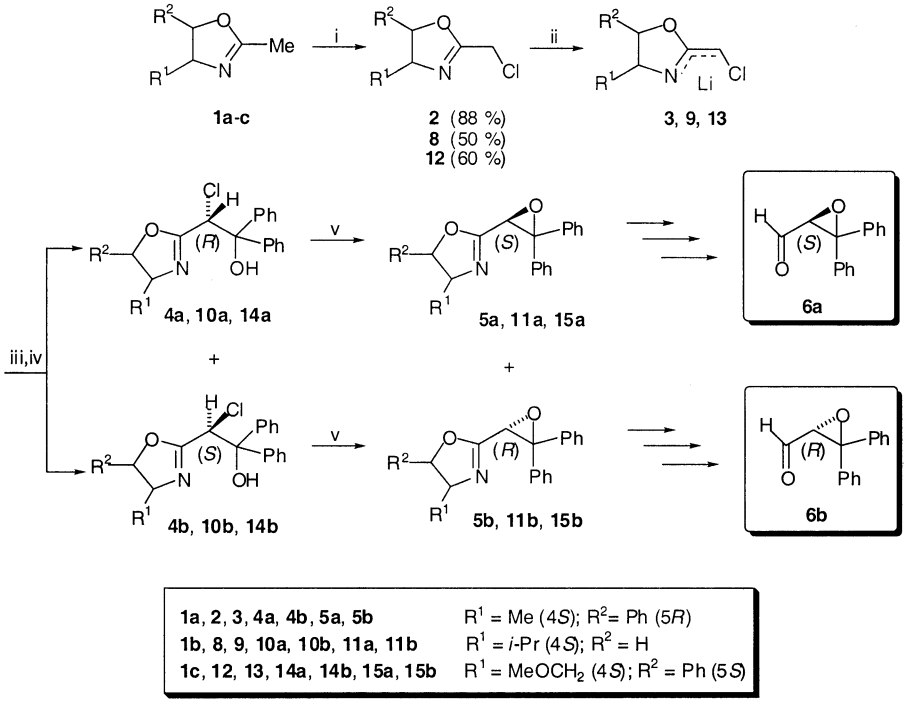
Abstract—Optically pure chloromethyloxazolines have been prepared, lithiated and then reacted with benzophenone to furnish stereoselectively oxazolinyl oxiranes and formyl oxiranes. The stereoselection observed has been related to the geometry of the intermediate lithium azaenolates. Calculations have been carried out in order to evaluate the relative stability of the *E* and *Z* forms of the lithium azaenolates. The reaction of a lithium azaenolate with other ketones leading to oxazolinyl epoxides is also reported. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

We have recently reported an oxazoline-mediated synthesis of formyl oxiranes which was based on the reaction of lithiated 2-chloromethyloxazoline with carbonyl compounds, conversion of the resulting chlorohydrins into the corresponding oxiranes and deblocking of the oxazoline moiety.[1]



Scheme 1. *Reagents and conditions*: (i) *t*-BuOCl, CCl_4; (ii) LDA, −78°C; (iii) Ph_2CO; (iv) H^+; (v) NaOH/*i*-PrOH.

Keywords: lithium and compounds; enolates; oxazolines; epoxides; computer-assisted methods.
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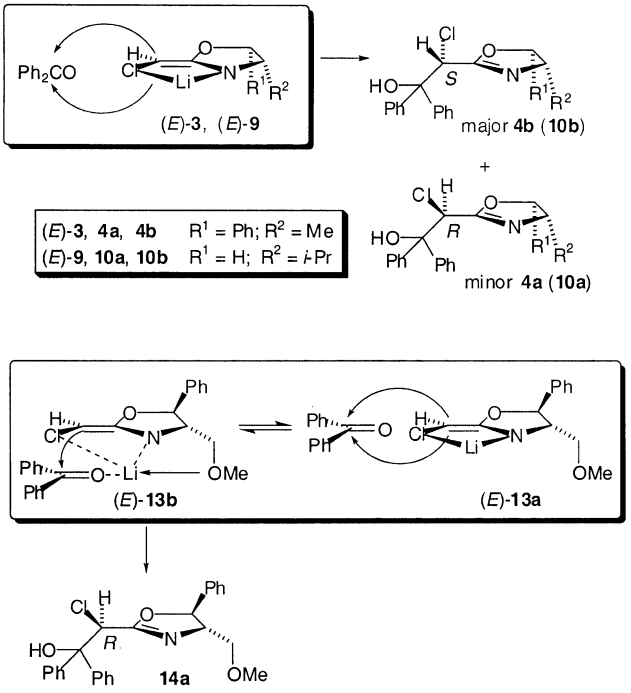


Scheme 2.

As oxazolinyl and formyl oxiranes are useful intermediates for the preparation of a large variety of compounds,[2–7] we decided to extend the above synthetic strategy to the preparation of optically active oxazolinyl and formyl oxiranes starting from chiral oxazolines.[8] We performed semiempirical and ab initio calculations on the carbanionic species in order to rationalize the stereoselective paths. Both the synthetic and calculation results are presented in this paper.

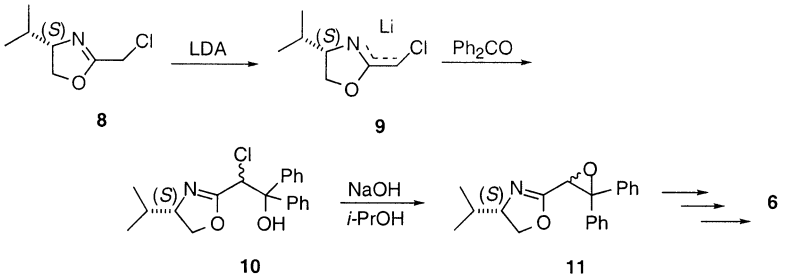
2. Results and discussion

2.1. Synthesis

Chlorination[9] of 2,4-dimethyl-5-phenyl-2-oxazoline **1a**[10] (Scheme 1) with *t*-butyl hypochlorite[11] in CCl_4 at room temperature afforded oxazoline **2** which was purified by flash chromatography.[12] Treatment of **2** (Scheme 1) with lithium diisopropylamide (LDA) at −78°C in THF furnished lithiated derivative **3**, which was stable at low temperature and could be kept there for at least 1 h. The reaction of **3** with benzophenone provided diastereomeric chlorohydrins **4a** and **4b** (74% yield; dr **4a/4b**=1:1.6) which could be separated by column chromatography (Scheme 1). The configuration of **4a** was proved to be *R* at Cα on the basis of the X-ray analysis. Therefore, that of **4b** at the same carbon should be *S*. Chlorohydrins **4a** and **4b**, which presumably exist intramolecularly hydrogen-bond associated[13,14] (Chart 1), could quantitatively and stereospecifically be converted into the oxazolinyl oxiranes **5a** and **5b**, respectively, upon treatment with NaOH. The oxazolinyl ring of **5a** and **5b** was then elaborated according to a known protocol[1] to give highly enantiomerically pure formyl epoxides **6a** (72% yield; *S*, ee%=91) and **6b** (93% yield; *R*, ee%>99), respectively (Scheme 1).

The poor stereoselection of the reaction of **3** with benzophenone, which leads at the end to **6**, might be explained by considering that the stereoselective determining step is the lithium azaenolate formation (deprotonation of the diastereotopic hydrogens at the chlorine bearing carbon atom to give the geometric isomers (*E*)-**3** and (*Z*)-**3**). These isomers, which are supposed not to interconvert,[15] should be of quite different energy on the basis of semiempirical calculations[16] (see ahead) which indicate that the *E* isomer is by far (about 25 kcal mol^{-1}) more stable than the corresponding *Z* isomer, due to a favorable internal coordination of lithium between the chlorine and nitrogen atoms. In view

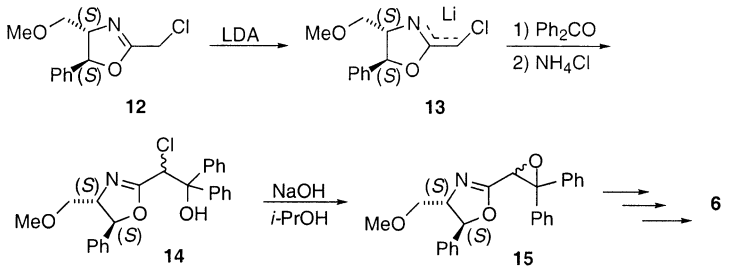
Table 1. Reaction of lithium azaenolate **9** with Ph_2CO in various solvents



Solvent	Reaction time (min)	Epoxides **11** (% yield)[a]	Formyl epoxides **6** (% yield)[a]	ee (%)[b]	Prevalent configuration of **6**
THF	15	74	83	37	*R*
TBME	15	69	83	21	*R*
Toluene	15	65	83	12	*R*
Hexane	15	58	83	21	*R*
DME	15	84	83	18	*R*
Et_2O	30	70	83	21	*R*
THP	15	88	83	25	*R*

[a] Isolated yields for each individual step. Quantitative conversion from chlorohydrins **10**.
[b] ee refers to formyl epoxides **6**; determined by GC on a chiral stationary phase (see Section 4).

Table 2. Reaction of **13** with Ph_2CO in various solvents



Solvent	Reaction time (min)	Epoxides **15** (% yield)[a]	Formyl epoxides **6** (% yield)[a]	ee (%)[b]	Prevalent configuration of **6**
THF	30	78	70	33	*S*
Et_2O	30	93	70	30	*S*
THP	40	88	70	24	*S*
Hexane	30	78	70	15	*S*
DME	40	24	70	31	*R*
Toluene	30	84	70	3	*R*

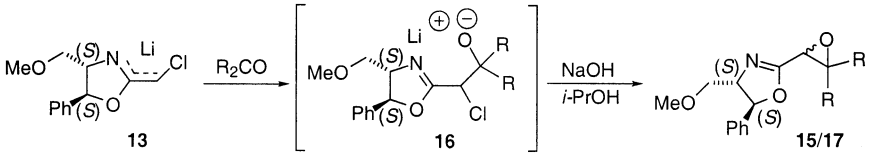
[a] Isolated yields for each individual step. Quantitative conversion from chlorohydrins **14**.
[b] ee refers to formyl epoxides **6**; determined by GC on a chiral stationary phase (see Section 4).

of such a computed large energy difference, we presume that the *E* species predominates by far in the solution.[17] The poor diastereoselection of the reaction of **3** with benzophenone to give chlorohydrins **4a** and **4b**, therefore, could be explained by assuming that the attack of the carbonyl compound to (*E*)-**3**, which has a planar arrangement, takes place on either the re and *si* faces with a slight predominance of the *si* face due to some steric hindrance exerted by the substituents on the oxazoline ring. The Ph and Me substituents, however, are rather far (>4.5 Å) from the carbanionic carbon (nucleophilic site) so that they are not expected to significantly affect the approach of the carbonyl compound) to give chlorohydrin **4b** (*S*,*R*,*S* configuration) as the major product (Scheme 2).

Lithiated oxazoline **9** (Scheme 1), prepared by lithiation of oxazoline **8**,[18] reacted cleanly with benzophenone affording diastereomeric chlorohydrins **10a** and **10b** (87% yield; dr **10a/10b**=1:2.2) that could be separated by column chromatography and assigned the configuration by IR, NMR and confirmed by an X-ray analysis carried out on **10a**. On this basis it was assigned the *R* configuration at the α-carbon. Consequently, diastereomer **10b** was assigned the *S* configuration at the same α-carbon. As in the case of **3**, the observed poor diastereoselection of the reaction of **9** with benzophenone to give chlorohydrins **10a** and **10b** could be rationalized by assuming that the predominant (*E*)-**9** isomer is attacked by the carbonyl compound prevalently on the *si* face (opposite to the isopropyl group) for steric reasons (Scheme 2). Isomers **10a** and **10b** were, then, treated with NaOH to give, stereospecifically, epoxides **11a** and **11b**, having the *S* and the *R* configuration, respectively, at the α-carbon.

The stereoselection observed in the reactions of lithiated

Table 3. Reaction of lithium azaenolate **13** with ketones



	Compound	Method[a]	Oxazolinyl epoxide[b] (% yield)	dr[c]
R=Ph–	**15**	A	78	33/67
		B	77	45/55
R=*p*-Cl–C_6H_4–	**17a**	A	70	46/54
		B	40	45/55
R,R=–$(CH_2)_5$–	**17b**	A	85	44/56
		B	50	47/53
R,R=–$(CH_2)_{11}$–	**17c**	A	73	56/44
		B	78	38/62
R,R=2-Adamantylidene	**17d**	A	90	66/33
		B	78	–

[a] **Method A**: A THF solution of 2-(chloromethyl)oxazoline (1 mmol) and ketone (1.3 mmol) was added dropwise at −90°C to a LDA solution (1.3 mmol) (Barbier's technique); the reaction mixture was quenched with sat. aq. NH_4Cl after 30 min. **Method B**: A THF solution of 2-(chloromethyl)oxazoline (1 mmol) was added dropwise at −90°C to a LDA solution (1.3 mmol); the resulting red solution was stirred for 45 min at −90°C and then a THF solution of ketone (1.3 mmol) was added dropwise. The reaction mixture was finally quenched with sat. aq. NH_4Cl after 30 min.
[b] The crude mixture of chlorohydrins was quantitatively converted to oxazolinyl epoxides whose isolated yields were reported.
[c] Diastereomeric ratio from ^1H NMR.

Table 4. PM3 and DFT Relative energies of isolated lithium azaenolates **3**, **9** and **13** and solvated lithium azaenolate **9**

Species	PM3	DFT
Planar[a] (*E*)-**3**	0.0	
Bridged[b] (*Z*)-**3**	+24.9	
Planar[a] (*Z*)-**3**	+25.0	
Planar[a] (*E*)-**13**[c]	0.0	
(*Z*)-**13**	+23.2	
Planar[a] (*E*)-**9**	0.0	0.0
Bridged[b] (*Z*)-**9**	+26.3	+6.9
Planar[a] (*Z*)-**9**	+24.7	+16.4
Planar[a] (*E*)-**9**·2Me_2O	0.0	
Bridged[b] (*Z*)-**9**·2Me_2O	+23.2	
Planar[a] (*Z*)-**9**·2Me_2O	+21.7	

Single-point B3LYP/6-31+G*/6-31G*//PM3 calculations, with the additional keywords 5D and SCF=TIGHT. Energies in kcal mol^{-1}.

[a] The lithium cation is approximately placed in the plane N–C_2–C_α–Cl.

[b] The lithium cation is placed out of the plane N–C_2–C_α–Cl, on the other side with respect to substituents in the 4- and 5-position (Li–N–C_2–C dihedral angles −27.6°).

[c] The case of lithium azaenolate **13** is handled separately due to the presence of additional intramolecular interactions (see text and Table 6).

oxazoline **9** with Ph_2CO decreased to some extent on going from ethereal to hydrocarbon solvents which may be due to different degrees of aggregation of the lithiated species (Table 1).

Oxazoline **12** (Scheme 1) has been prepared by chlorination of commercially available oxazoline **1c** with *t*-butyl hypochlorite according to a procedure similar to that followed for oxazoline **2**.[19] Compound **12** was substantially pure and did not need further purification for the metalation reaction (see below). In any case, attempted purification by column chromatography on silica gel caused ring cleavage to give (quantitative conversion) the hydroxy amide **7b** (one stereoisomer), whose structure was established by IR, $^1H/^{13}C$ NMR and GC-MS analysis (Chart 1).

Metalation of **12** (Scheme 1) gave a dark red solution of lithiated oxazoline **13**, that was trapped with benzophenone affording an inseparable mixture of chlorohydrins **14a** and **14b** (dr **14a/14b**=2:1 by ^1H NMR). Here again the coupling reaction of **13** with benzophenone occurred with poor diastereoselection. The mixture of **14a** and **14b** was then reacted with NaOH in *i*-PrOH to give diastereomeric oxazolinyl oxiranes **15a** and **15b** that could not be separated. On standing on silica gel for long time oxiranes **15a** and **15b** underwent ring cleavage of the oxazolinyl moiety to furnish oxiranyl hydroxy amides **16a** and **16b** (Chart 1) which were separated by crystallization (hexane). Their structures were established by IR, NMR and GC-MS analysis. The configuration at the oxiranyl carbon of **16a** was proved to be *R* by X-ray analysis.

The elaboration of the oxazoline moiety of **15a** and **15b** provided enantiomerically enriched formyl epoxide **6a** (ee%=33) (see Section 4 and Table 2). Comparable values of ee were obtained in solvents such as Et_2O and tetrahydropyran (THP). Lower ee values (15%) were observed in hexane. There was no enantioselection in toluene. In DME the reaction led, instead, to **6b** (ee%=31) (see Table 2). Unfortunately, at present we do not have a plausible explanation for such changing ee values. It is worth noting

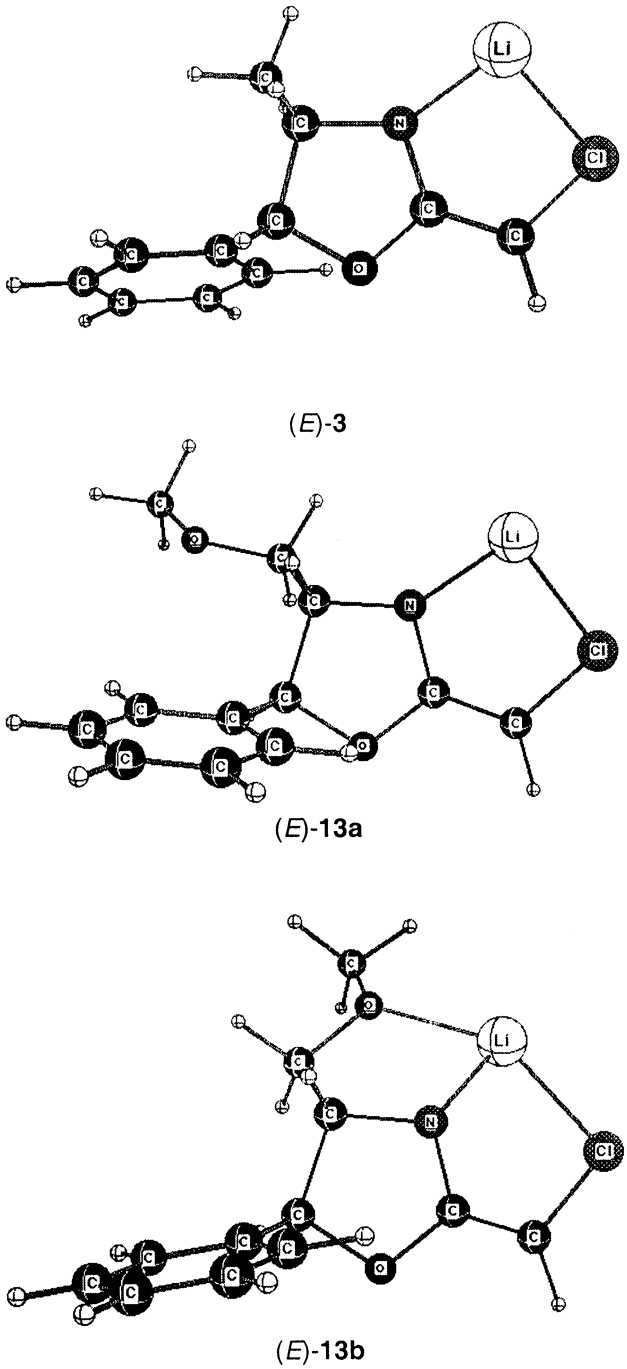


Figure 1. Planar lithium azaenolates (*E*)-**3**, (*E*)-**13a**, and lithium azaenolate (*E*)-**13b** showing a MeO–Li coordination (dihedral angle Li–N–C(2)–C(α)=+25°).

that the reaction of **13** with benzophenone, ending up with the formation of formyl oxiranes **6**, proceeded in a stereoselective manner (low) but opposite to that observed in the reactions of **3** and **9**.

A comparable diastereoselectivity was observed in the reaction of lithium azaenolate **13** with other ketones in THF (Table 3). The kind of stereoselection was not time dependent. Indeed, the same diastereomeric ratio of the related chlorohydrins was observed when the lithium azaenolate **13** was reacted with ketones soon after its

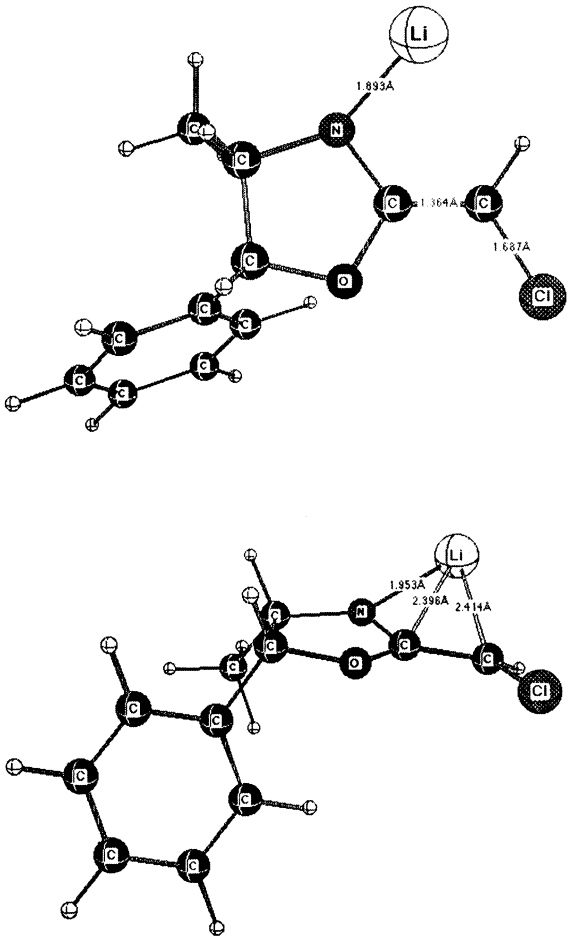


Figure 2. Planar and bridged lithium azaenolate (*Z*)-**3**.

generation (Barbier conditions) or after 45 min from its generation.

2.2. Computational investigations

In an effort to provide an explanation for the modest diastereoselection of the reaction of lithium azaenolates **3**, **9** and **13** with benzophenone we decided to do some calculations.[20–25] Table 4 collects PM3 relative energies of the geometry optimized lithium azaenolates (*E*)-**3** and (*Z*)-**3**. PM3 geometry optimization of (*E*)-**3** shows an almost planar arrangement along the sequence Li–N–C_2–C–Cl (Fig. 1). In contrast, we found two energy minimum geometries for the corresponding *Z* isomer: a planar and a bridged arrangement (see Fig. 2).[26] Semiempirical calculations indicate that the *E* isomer is more stable than the corresponding *Z* isomer. PM3 *E*–*Z* relative energies range around 25 kcal mol^{-1}. Such a higher stability of the *E* species has to be ascribed to a favorable internal coordination of lithium between the chlorine and the nitrogen atoms. Therefore, calculations do support the hypothesis made above according to which the modest stereoselection of the reaction of **3** with benzophenone is to be ascribed to the fact that the more abundant geometric isomer (*E*)-**3**, having a planar arrangement with lithium chelated between the nitrogen and chlorine atoms, can be attacked by the ketone on both faces (re and *si* faces) with only a slight preference of that opposite to the phenyl and the methyl groups (*si* face), which, however, are rather far from the reactive center to exert a significant steric effect.

Table 5. Solvation energies of lithium azaenolate **9**

Species	Solvation energy (kcal mol^{-1})[a]
Planar (*E*)-**9**	−16.7
Bridged (*Z*)-**9**	−19.7
Planar (*Z*)-**9**	−19.6

PM3.
[a] Values refer to the process of solvation of the free lithium azaenolate species with two molecules of Me_2O.

Semiempirical calculations were confirmed both considering the role of the solvent and using ab initio energy computations, as we did for the case of azaenolate **9** (Tables 4 and 5). With reference to lithiated oxazoline **9**, PM3 *E*–*Z* relative energies ranged between 24.7 and 26.3 kcal mol^{-1} while the DFT values were computed lower but in the same direction. The computed higher stability of the *E* isomer, with respect to the *Z* species, was verified in the presence of the solvent effect.[27] Conclusions of computations performed in absence of solvent are essentially confirmed, with the *E* lithium azaenolate being by far the most stable. As in the case of lithiated oxazoline **3**, the poor stereoselection of the coupling reaction of **9** with benzophenone has to be put in relation with the geometry of the lithium azaenolate (mainly (*E*)-**9**) and the feeble steric effect of the isopropyl group.

PM3 optimizations of the *E* isomer of lithiated oxazoline **13** resulted in two energy minimum geometries, (*E*)-**13a** and (*E*)-**13b** (Fig. 1). Both geometries present internal coordination of lithium between the chlorine and nitrogen atoms, as already obtained for (*E*)-**3** and (*E*)-**9**. In the most stable (PM3) (*E*)-**13a** isomer, the lithium ion is preferably placed in the plane of the π-system and no additional internal coordination involving the methoxy group is observed. The second computed geometry (*E*)-**13b**, less stable by 3.6 kcal mol^{-1}, shows MeO–Li coordination. Electron density calculations confirm the occurrence of the internal coordination MeO–Li.[28] In this case the lithium ion is located in the same face occupied by the methoxy group; actually, a preliminary coordination with the carbonyl group of the electrophile could lead to some degree of selectivity, with preferential formation of chlorohydrin (*R*)-**14a**. Since the semiempirical approach could not be appropriate to describe adequately the weak intramolecular binding energies, we decided to calculate energies at the DFT level (Table 6). The high-level ab initio computations now predict that the intramolecular coordinated (MeO–Li) isomer (*E*)-**13b** is more stable[29] than the (*E*)-**13a** isomer (no MeO–Li coordination) by about 1.2 kcal mol^{-1}.

Table 6. PM3 and DFT Relative energies of (*E*)-**13** isomers

Compound	PM3	DFT
(*E*)-**13a**	0.0	+1.2
(*E*)-**13b**	+3.6	0.0

Single-point B3LYP/6-31+G*/6-31G*//PM3 calculations, with the additional keywords 5D and SCF=TIGHT. In order to properly compute the non bonding interactions, diffuse functions were included for Li, N and O atoms (6-31+G*). Energies in kcal mol^{-1}.

The (*Z*)-**13** isomer, in which the lithium coordination by the chlorine atom is not feasible, presents a favored MeO–Li interaction, with the lithium ion placed out of the plane. This geometry would be the favored one in the absence of the chlorine atom in the α position. Therefore, should the (*Z*)-**13** isomer be present in solution, the attack of the carbonyl compound would occur on the face opposite to the phenyl group via a preliminary coordination between the oxygen of the carbonyl and lithium. In principle, a pronounced stereoselection in favor of the chlorohydrin (*R*)-**14a** should be expected and this was not the case.

On the basis of such indications, in order to explain the low stereoselection of the conversion of **12** into **6** we assume that the predominant isomer (*E*)-**13** is present in solution as a mixture of the two forms (*E*)-**13a** and (*E*)-**13b**. The carbonyl compound would attack the (*E*)-**13a** isomer either from the top or from the bottom thus showing no or very poor stereoselection. The (*E*)-**13b** isomer, instead, would be attacked by the carbonyl compound preferentially on its *re* face via a transition state in which the lithium is coordinated by the methoxy group and the oxygen of the carbonyl (Scheme 2). Therefore, the observed preferential formation of the 2*R*,4′*S*,5′*S* chlorohydrin (leading to the 2*S*,4′*S*,5′*S* oxazolinyl oxirane and then to the *S* formyl oxirane) could be rationalized by assuming the contribution to the stereochemistry of the coupling reaction of both the isomers (*E*)-**13a** and (*E*)-**13b**.

Therefore, the semiempirical and DFT investigation have pointed out that the stereochemistry of the coupling reaction of lithiated oxazoline **13** (by far *E* configurated) is only in some extent determined by the steric effect of the C_5 phenyl group and the coordinating ability of the C_4 methoxy group.

3. Conclusion

In conclusion, this paper reports some so far undescribed aspects of the oxazolines chemistry. Indeed, while the chemistry of 2-alkyloxazolines has been deeply investigated, that of the halogenoalkyl derivatives has not. Our work has demonstrated that of the two geometrical forms of lithium azaenolates of chiral chloroalkyloxazolines, those adopting the *E* configurations are by far more stable than the *Z* ones due to the intramolecular chelation of lithium cation between the chlorine and nitrogen atoms. This sounds interesting if one considers that in the lithiation reaction of 2-alkyloxazolines the two kinetic azaenolates form in approximately 95:5 ratio in favor of the *Z* isomer.[17] In the coupling reactions of **3**, **9** and **13** with carbonyl compounds, steric and coordination effect of substituents at the positions 4 and 5 of the oxazoline ring is only modest, mainly due to their distance from the carbanionic center (the α-carbon). With substituents capable only of some steric effect the attack of the carbonyl compound to the azaenolate preferably occurs from the opposite side (*si* face), while with coordinating substituents from the same side (*re* face). Although the reactions of the above azaenolates with carbonyl compounds are not highly stereoselective, chlorohydrins can be separated and stereospecifically transformed into optically active formyl oxiranes. More work is worth doing in order to establish which metal azaenolates[30] are suitable for a high stereoselection. This is under way in our lab and results will be reported in due course.

4. Experimental

4.1. General

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under a nitrogen atmosphere over sodium benzophenone ketyl. Dry tetrahydropyran (THP), hexane, 1,2-dimethoxyethane (DME), toluene, *tert*-butyl methyl ether (TBME), CCl_4, (1*R*,2*S*)-(−)-norephedrine, L-2-amino-3-methyl-1-butanol, ethyl acetimidate hydrochloride, (4*S*,5*S*)-(−)-4-methoxymethyl-2-methyl-5-phenyl-2-oxazoline and all other chemicals were of commercial grade (Aldrich) and used without further purification. *tert*-Butyl hypochlorite was prepared according to the literature.[11] TMEDA and diisopropylamine were distilled over finely powdered calcium hydride. Petroleum ether refers to the 40–60°C boiling fraction. Commercial solution of *n*-BuLi (in hexanes) from Aldrich was titrated by using *N*-pivaloyl-*o*-toluidine prior to use.[31] For the ^{1}H- and ^{13}C NMR spectra (^{1}H 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 5995C (dimethylsilicon capillary column, 30 m, 0.25 mm ID) 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/diethyl ether (or AcOEt) mixture as the eluent. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

4.2. Enantiomeric purity analysis

Enantiomeric purity assays were carried out with both racemic and optically active substrates on a GC equipped with a permethylated β-cyclodextrin (β-DEX 120, Supelco) (30 m×0.25 mm ID×0.25 μm film thickness) fused silica capillary column as stationary phase. Det.: FID, 300°C. Column head pressure: 20 psi. Oven: 150°C. Sample: 1 μL, 500 μg mL^{-1} each in methylene chloride. (2*S*)-(**6a**): t_R=83.39 min; (2*R*)-(**6b**): t_R=86.61 min.

4.2.1. Preparation of (4*S*,5*R*)-(−)-2,4-dimethyl-5-phenyl-2-oxazoline (1a). To a stirred milky solution of ethyl acetimidate hydrochloride (2.17 g, 17.60 mmol) in dry CCl_4 (15 mL), at 0°C, a solution of (1*R*,2*S*)-(−)-norephedrine (2.00 g, 13.23 mmol) in dry CCl_4 (12 mL) was added dropwise. The resulting mixture was stirred overnight at room temperature and poured into 50 mL of 2% $NaHCO_3$. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3×20 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The crude product was purified by flash chromatography (AcOEt) to give 1.97 g (85% yield) of a colorless oil. $[\alpha]_D$=−246 (*c* 1 $CHCl_3$) [lit.,[10b] $[\alpha]_D$=−247 (*c* 3.43 $CHCl_3$)]. ^{1}H and ^{13}C NMR spectroscopical data are similar

to those reported in Ref. 10b. GC-MS (70 eV); *m/z* (%): 175 (4.2, M^+), 105 (6.9), 77 (11.0), 69 (100.0), 68 (27.1), 42 (43.5). FTIR (film, cm^{-1}): 3033, 2975, 1678 (C=N), 1385, 1226, 979, 700.

4.2.2. Preparation of (4*S*,5*R*)-(−)-2-chloromethyl-4-methyl-5-phenyl-2-oxazoline (2). *tert*-Butyl hypochlorite (859 mg, 7.92 mmol) was added dropwise to a stirred solution of (4*S*,5*R*)-(−)-2,4-dimethyl-5-phenyl-2-oxazoline (**1a**) (1.26 g, 7.20 mmol) in anhydrous CCl_4 (25 mL), under N_2 at an ice-bath temperature. After 30 min the ice-bath was removed and the reaction mixture was stirred at room temperature for 3 h. The solvent was removed by rotary evaporator under reduced pressure and the crude product purified by flash chromatography (AcOEt/petroleum ether 8/2). Oxazoline **2** was isolated in 88% yield as a pale oil. Small amounts of **7a**, that could form on standing on silica gel, can be removed by washing the product with cold hexane. $[\alpha]_D=-253.6$ (*c* 1 $CHCl_3$) [lit.,[11] $[\alpha]_D=-269$ (*c* 3.68 $CHCl_3$)]. ^1H and ^{13}C NMR spectroscopical data are similar to those reported in Ref. 11. GC-MS (70 eV); *m/z* (%): 211 (2.7, M^++2), 209 (8.1, M^+), 132 (7.3), 105 (32.6), 103 (73.6), 68 (100.0), 41 (234). FTIR (film, cm^{-1}): 3032, 2978, 1670 (C=N), 1455, 1344, 978, 746, 701.

4.2.3. Preparation of chlorohydrins 4a and 4b. A solution of 16.74 mmol of lithium diisopropylamide (LDA) (from 2.34 mL of diisopropylamine and 10.84 mL of 1.54 M *n*-BuLi in 15 mL of dry THF) was prepared under N_2 and stirred at 0°C for 15 min. To this solution, cooled at −100°C with a methanol–liquid nitrogen bath, a mixture of (4*S*,5*R*)-(−)-2-chloromethyl-4-methyl-5-phenyl-2-oxazoline (**2**) (2.50 g, 11.96 mmol) and benzophenone (2.39 g, 13.16 mmol) in 50 mL of dry THF was added dropwise over a 2 h period and the resulting yellow solution was stirred at this temperature for 15 min. Then the reaction mixture was quenched (at −100°C), with sat. aq. NH_4Cl and extracted with Et_2O (3×30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt: 9/1) to give **4a** and **4b** (74% overall and isolated yield; dr **4a/4b** 1:1.6, from ^1H NMR) which showed the following data:

(2R,4′S,5′R)-(−)-2-Chloro-1,1-diphenyl-2-(4-methyl-5-phenyl-2-oxazolin-2-yl)ethan-1-ol (**4a**): Colorless prismatical bipyramidal crystals, mp 112–113°C (hexane). $[\alpha]_D=-105.2$ (*c*1 $CHCl_3$). dr 96:4 (from ^1H NMR) ^1H NMR (300 MHz): δ=0.39 (d, *J*=7.0 Hz, 3H, C*H*$_3$), 4.36–4.46 (m, 1H, C*H*CH$_3$), 5.51 (s, 1H, C*H*Cl), 5.54 (d, *J*=10.1 Hz, 1H, C*H*Ph), 6.18 (s, 1H, exchanges with D_2O, O*H*), 6.69–6.71 (m, 2H, aromatic *H*), 7.18–7.37 (m, 9H, aromatic *H*), 7.59–7.64 (m, 4H, aromatic *H*). ^{13}C NMR (APT, 50.3 MHz): δ=16.8 (*C*H$_3$), 56.1, 64.3, 78.8 (*C*–OH), 84.7, 125.7 (Ar*C*H), 125.8 (Ar*C*H), 126.1 (Ar*C*H), 126.5 (Ar*C*H), 127.3 (Ar*C*H), 127.5 (Ar*C*H), 127.6 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.5 (Ar*C*H), 135.1 (Ar*C*), 142.6 (Ar*C*), 144.3 (Ar*C*), 165.1 (*C*=N). GC-MS (70 eV); *m/z* (%): 211 (4.2, M^++2−Ph_2CO), 209 (8.1, M^+−Ph_2CO), 132 (9.1), 105 (31.4), 103 (76.0), 68 (100.0) 41 (22.4). FTIR (KBr, cm^{-1}): 3362 (broad, OH), 1667 (C=N), 1450, 1383, 1193, 1091, 1000, 958, 751, 704, 638. Anal. Calcd for $C_{24}H_{22}ClNO_2$: C 73.56, H 5.66, N 3.57. Found C 73.36, H 5.77, N 3.46.

(2S,4′S,5′R)-(−)-2-Chloro-1,1-diphenyl-2-(4-methyl-5-phenyl-2-oxazolin-2-yl)ethan-1-ol (**4b**): White needles, mp 126–129°C (hexane). $[\alpha]_D=-182$ (*c* 1, $CHCl_3$). dr>99% (from ^1H NMR) ^1H NMR (300 MHz): δ 0.63 (d, *J*=7.0 Hz, 3H, C*H*$_3$CH), 4.23–4.33 (m, 1H, C*H*CH$_3$), 5.48 (d, *J*=9.9 Hz, C*H*Ph), 5.56 (s, 1H, C*H*Cl), 5.78 (s, 1H, exchanges with D_2O, O*H*), 7.03–7.06 (m, 2H, aromatic *H*), 7.20–7.35 (m, 9H, aromatic *H*), 7.56–7.60 (m, 4H, aromatic *H*). ^{13}C NMR (APT, 50.3 MHz): δ=16.9 (*C*H$_3$), 57.5 (*C*HCH$_3$), 64.5 (*C*HPh), 78.6 (*C*–OH), 84.5 (*C*HCl), 125.6 (Ar*C*H), 126.1 (Ar*C*H), 127.2 (Ar*C*H), 127.5 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 128.5 (Ar*C*H), 135.5 (Ar*C*), 144.8 (Ar*C*), 164.5 (*C*=N). GC-MS (70 eV); *m/z* (%): 211 (3.4, M^++2−Ph_2CO), 209 (11.1, M^+−Ph_2CO), 132 (8.9), 105 (33.5), 103 (80.1), 68 (100.0), 41 (22.9). FTIR (KBr, cm^{-1}): 3229 (broad, OH), 1662 (C=N), 1454, 1378, 1089, 953, 750, 706. Anal. Calcd for $C_{24}H_{22}ClNO_2$: C 73.56, H 5.66, N 3.57. Found C 73.45, H 5.64, N 3.26.

4.2.4. Preparation of oxazolinyl epoxides 5a and 5b. The chlorohydrins **4a** and **4b** were cyclized quantitatively to epoxides **5a** and **5b**, respectively, in NaOH/*i*-PrOH.[32] The latter were purified by flash chromatography (silica gel; petroleum ether/AcOEt: 9:1) and showed the following data:

(2S,4′S,5′R)-(−)-2-(3,3-diphenyloxiranyl)-4-methyl-5-phenyl-2-oxazoline (**5a**): Oil. $[\alpha]_D=-112.0$ (*c* 1 $CHCl_3$). ^1H NMR (90 MHz): δ=0.60 (d, *J*=7.0 Hz, 3H, C*H*$_3$), 4.13–4.50 (m overlapping s at 4.23, 1H, C*H*CH$_3$), 4.23 (s, 1H, C*H* epoxide), 5.66 (d, *J*=10.0 Hz, 1H, C*H*Ph), 6.50–6.77 (m, 2H, aromatic *H*), 7.27–7.87 (m, 13H, aromatic *H*). ^{13}C NMR (125 MHz): δ=17.7 (*C*H$_3$), 59.9, 65.0, 66.3, 125.7 (Ar*C*H), 126.6 (Ar*C*H), 127.5 (Ar*C*H), 127.9 (Ar*C*H), 128.1 (Ar*C*H), 128.2 (Ar*C*H), 128.3 (Ar*C*H), 128.41 (Ar*C*H), 128.43 (Ar*C*H), 135.6 (Ar*C*), 136.0 (Ar*C*), 139.0 (Ar*C*), 161.4 (C=N). GC-MS (70 eV); *m/z* (%): 355 (12.1, M^+), 338 (13.3), 248 (15.6), 238 (28.8), 208 (28.1), 165 (61.5), 118 (100.0), 105 (26.8), 77 (22.8), 67 (15.4). FTIR (film, cm^{-1}): 2975, 1656 (C=N), 1542 (1450), 1079, 755, 702. Anal. Calcd for $C_{24}H_{21}NO_2$: C 81.10, H 5.96, N 3.94. Found C 80.98, H 5.91, N 3.93.

(2R,4′S,5′R)-(−)-2-(3,3-diphenyloxiranyl)-4-methyl-5-phenyl-2-oxazoline (**5b**): Oil. $[\alpha]_D=-95.0$ (*c* 1, $CHCl_3$). ^1H NMR (90 MHz): δ=0.37 (d, *J*=7.0 Hz, 3H, C*H*$_3$), 4.07–4.50 (m overlapping s at 4.20, 1H, C*H*CH$_3$), 4.20 (s, 1H, C*H* epoxide), 5.37 (d, *J*=10.0 Hz, 1H, C*H*Ph), 6.87–7.72 (3m, 15H, aromatic *H*). ^{13}C NMR (APT, 50.3 MHz): δ=17.1 (*C*H$_3$), 58.9, 64.9, 66.8 (*C*Ph$_2$), 84.6, 126.0 (Ar*C*H), 127.3 (Ar*C*H), 127.7 (Ar*C*H), 127.9 (Ar*C*H), 128.08 (Ar*C*H), 128.12 (Ar*C*H), 128.2 (Ar*C*H), 128.4 (Ar*C*H), 135.6 (Ar*C*), 136.0 (Ar*C*), 138.8 (Ar*C*), 160.6 (*C*=N). GC-MS (70 eV); *m/z* (rel.int.): 355 (5.8, M^+), 338 (8.2), 248 (15.8), 238 (28.0), 208 (26.7), 165 (61.4), 118 (100.0), 105 (27.5), 77 (25.1), 67 (16.2). FTIR (film, cm^{-1}): 3408, 1647 (C=N), 1540, 1448, 1219, 1089, 703. Anal. Calcd for $C_{24}H_{21}NO_2$: C 81.10, H 5.96, N 3.94. Found C 80.95, H 5.93, N 3.94.

4.2.5. Deblocking of oxazolinyl epoxides 5a and 5b to (2*S*)-3,3-diphenyl-oxirane-2-carbaldehyde (6a) and (2*R*)-3,3-diphenyl-oxirane-2-carbaldehyde (6b). To a solution of oxazolinyl epoxide (**5a** or **5b**) (443 mg, 1.25 mmol) in dry CH_2Cl_2 (8.5 mL), under N_2 at 0°C, methyl triflate (1.75 mmol, 197.6 μL) was added directly. The resulting solution was stirred for 30 min at 0°C; then it was allowed to cool to −78°C with a methanol–liquid nitrogen bath and a solution of $NaBH_4$ (29.5 mg) in dry THF (5.5 mL)/dry EtOH (1.38 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and stirred for 10 h in the case of **5a** (with 2 equiv. of $(COOH)_2{\cdot}2H_2O$ 1% w/w) and for only 30 min (with no oxalic acid) in the case of **5b**; then it was poured into 50 mL of water, extracted with Et_2O (3×10 mL) and the combined organic layers dried (Na_2SO_4). Concentration of the ethereal solution left an oil that was quickly flash-chromatographed (silica gel; petroleum ether/AcOEt: 9:1) (so removing also little quantities of benzophenone as degradation product) to give: (2*S*)-(**6a**) (72% yield) $[\alpha]_D=-38$ (*c* 1 $CHCl_3$). t_R=83.39 min. ee%=91; (2*R*)-(**6b**) (93% yield) $[\alpha]_D=+44.6$ (*c* 1 $CHCl_3$). t_R=86.61 min. ee%>99. Waxy solid, mp 70–72°C. ^{1}H NMR (90 MHz): δ=3.67 (d, *J*=6.0 Hz, 1H, C*H* epoxide), 7.23–7.50 (m, 10H, aromatic *H*), 8.92 (d, *J*=6.0 Hz, 1H, C*H*O). ^{13}C NMR (APT, 50.3 MHz): δ= 66.2 (*C*H), 67.5 (*C*Ph$_2$), 126.4 (Ar*C*H), 128.1 (Ar*C*H), 128.6 (Ar*C*H), 128.7 (Ar*C*H), 134.8 (Ar*C*), 138.5 (Ar*C*), 198.4 (*C*HO). GC-MS (70 eV); *m/z* (%): 224 (3.6, M^+), 223 (3.4), 207 (11.0), 195 (60.7), 179 (19.5), 165 (100.0), 105 (12.2), 77 (17.9). FTIR (film, cm^{-1}): 3044, 2922, 1711 (HC=O), 1444, 1261, 1083, 756, 694. Anal. Calcd for $C_{15}H_{12}O_2$: C 80.34, H 5.39. Found C 80.74, H 5.77.

4.2.6. Synthesis of chloromethyloxazolines 8 and 12. Their preparation was performed in the same manner as that of (4*S*,5*R*)-(−)-2-chloromethyl-4-methyl-5-phenyl-2-oxazoline (**2**) by using (4*S*)-4-isopropyl-2-methyl-2-oxazoline[18]**1b** and the commercially available (Aldrich) (4*S*,5*S*)-(−)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline **1c**, respectively. They showed the following data:

(4S)-(−)-2-Chloromethyl-4-isopropyl-2-oxazoline (**8**): Oil, 50%, bp 75°C/0.1 mbar. $[\alpha]_D=-97.8$ (*c* 5 $CHCl_3$). [lit.,[11] $[\alpha]_D=-97.9$ (*c* 2.69 $CHCl_3$)]. ^{1}H and ^{13}C NMR data are similar to those reported in Ref. 11. GC-MS (70 eV); *m/z* (%): 163 (0.2, M^++2), 161 (0.6, M^+), 120 (30.9), 119 (29.8), 118 (100.0), 92 (17.0), 90 (54.5), 55 (19.6), 54 (22.2), 43 (42.2), 41 (40.3). FTIR (film, cm^{-1}): 2955, 1666 (C=N), 1466, 1355, 1238, 977, 755.

(4S,5S)-(−)-2-Chloromethyl-4-methoxymethyl-5-phenyl-2-oxazoline (**12**): Oil, 60%. $[\alpha]_D=-84.1$ (*c* 12 $CHCl_3$). [lit.,[11] $[\alpha]_D=-84.6$ (*c* 3.37 $CHCl_3$)]. ^{1}H and ^{13}C NMR data are similar to those reported in Ref. 11. GC-MS (70 eV); *m/z* (%): 241 (0.2, M^++2), 239 (0.6, M^+), 194 (41.3), 146 (31.6), 119 (54.0), 105 (25.5), 104 (23.8), 103 (20.2), 102 (34.2), 98 (75.4), 91 (56.1), 45 (100.0). FTIR (film, cm^{-1}): 3027, 2915, 2814, 1666 (C=N), 1447, 1189, 1122, 976, 757, 695.

4.2.7. Preparation of chlorohydrins 10a and 10b. Their preparation was performed in the same manner as those of **4a** and **4b** by using in this case chloromethyloxazoline **8**. The two diastereomeric chlorohydrins so obtained, **10a** and **10b**, were separated by flash chromatography (silica gel; petroleum ether/AcOEt: 9:1) (87% overall and isolated yield; dr **10a/10b**=1:2.2, from ^{1}H NMR) and showed the following data:

(2R,4′S)-(+)-2-Chloro-1,1-diphenyl-2-(4-isopropyl-2-oxazolin-2-yl)ethan-1-ol (**10a**): White needles, mp 138–139°C (hexane). $[\alpha]_D=+37.47$ (*c* 1 $CHCl_3$). dr: 97/3 (from ^{1}H NMR). ^{1}H NMR (500 MHz): δ=0.49 and 0.54 (2×d, *J*=6.7 Hz, 2×3H, 2×C*H*$_3$), 1.25–1.34 (m, 1H), 3.83–3.91 (m, 2H), 4.20–4.23 (m, 1H), 5.38 (s, 1H), 6.26 (br s, 1H, exchanges with D_2O, O*H*), 7.13–7.24 (m, 2H, aromatic *H*), 7.26–7.34 (m, 4H, aromatic *H*), 7.54–7.61 (m, 4H, aromatic *H*). ^{13}C NMR (125 MHz): δ=17.5, 17.9, 31.9, 56.5, 70.2, 71.5, 78.5, 125.2, 125.4, 127.0, 127.1, 128.0, 128.3, 142.8, 145.4, 165.1. GC-MS (70 eV); *m/z* (%): 161 [0.73, M^+-Ph_2CO), 118 (100.0), 92 (18.7), 90 (57.7), 76 (7.4), 55 (38.0), 54 (38.6), 43 (76.5). FTIR (KBr, cm^{-1}): 3284 (broad, OH), 2954, 1661 (C=N), 1454, 1199, 1035, 942, 753, 696. Anal. Calcd for $C_{20}H_{22}ClNO_2$: C 69.86, H 6.45, N 4.07. Found C 69.52, H 6.27, N 4.30.

(2S,4′S)-(−)-2-Chloro-1,1-diphenyl-2-(4-isopropyl-2-oxazolin-2-yl)ethan-1-ol (**10b**): White needles, mp 127–128°C (hexane). $[\alpha]_D=-52.4$ (*c* 1, $CHCl_3$). dr>99% (from ^{1}H NMR). ^{1}H NMR (500 MHz): δ=0.77 and 0.81 (2×d, *J*= 6.8 Hz, 2×3H, 2×C*H*$_3$), 1.56–1.64 (m, 1H), 3.71–3.76 (m, 1H), 3.93 (like t, *J*=8.3 Hz, 1H), 4.13 (dd, *J*=8.5, 9.8 Hz, 1H), 5.40 (s, 1H), 5.99 (br s, 1H, exchanges with D_2O, O*H*), 7.14–7.22 (m, 2H, aromatic *H*), 7.23–7.32 (m, 4H, aromatic *H*), 7.45–7.56 (m, 4H, aromatic *H*). ^{13}C NMR (125 MHz): δ=18.0, 18.3, 32.8, 57.1, 70.3, 71.4, 78.7, 125.5, 125.7, 127.1, 127.2, 128.1, 128.3, 143.1, 144.8, 164.7. GC-MS (70 eV); *m/z* (%): 161 (0.7, M^+-Ph_2CO), 120 (34.2), 118 (100.0), 90 (35.8), 83 (15.4), 54 (8.6), 43 (15.1). FTIR (KBr, cm^{-1}): 3222 (broad, OH), 2965, 1651 (C=N), 1447, 1362, 1251, 1170, 1064, 967, 759, 696. Anal. Calcd for $C_{20}H_{22}ClNO_2$: C 69.86, H 6.45, N 4.07. Found C 69.47, H 6.32, N 3.68.

4.2.8. Preparation of oxazolinyl epoxides 11a and 11b. The chlorohydrins **10a** and **10b** were cyclized quantitatively to epoxides **11a** and **11b**, respectively, in NaOH/*i*-PrOH.[32] The latter were purified by flash chromatography (silica gel; petroleum ether/AcOEt: 7:3) and showed the following data:

(2S,4′S)-(−)-2-(3,3-Diphenyloxiranyl)-4-isopropyl-2-oxazoline (**11a**): White solid, mp 83–84°C (hexane). $[\alpha]_D=-8.67$ (*c* 1 $CHCl_3$). dr 97/3 (from ^{1}H NMR). ^{1}H NMR (500 MHz): δ=0.75 and 0.85 (2×d, *J*=6.8 Hz, 2×3H, 2×C*H*$_3$), 1.56–1.62 (m, 1H), 3.46 (like t, *J*=8.7 Hz, 1H), 3.76–3.81 (m, 1H), 4.06 (dd, *J*=8.5, 9.7 Hz, 1H), 4.08 (d, *J*=0.5 Hz, 1H), 7.22–7.34 (m, 8H, aromatic *H*), 7.42–7.46 (m, 2H, aromatic *H*). ^{13}C NMR (125 MHz): δ=18.0, 18.7, 32.1, 59.7, 66.2, 70.2, 72.3, 127.89, 127.93, 128.0, 128.2, 128.3, 135.7, 138.9, 161.7. GC-MS (70 eV); *m/z* (%): 307 (8.7, M^+), 290 (29.6), 278 (11.0), 208 (100.0), 165 (57.2), 152 (5.6), 105 (9.4), 105 (26.8), 77 (7.0). FTIR (KBr, cm^{-1}): 3059, 2955, 1658 (C=N), 1453, 1263, 985, 781, 761, 703. Anal. Calcd for $C_{20}H_{21}NO_2$: C 78.15, H 6.89, N 4.56. Found: C 78.42, H 7.21, N 4.34.

(2R,4′S)-(−)-2-(3,3-diphenyloxiranyl)-4-isopropyl-2-oxazoline (**11b**): Oil. $[\alpha]_D=-51.3$ (*c* 0.33 $CHCl_3$). dr 97/3 (from

^{1}H NMR). ^{1}H NMR (500 MHz): δ=0.64 and 0.69 (2×d, J=6.7 Hz, 2×3H, 2×CH_3), 1.30–1.40 (m, 1H), 3.73–3.82 (m, 2H), 3.90–3.96 (m, 1H), 4.04 (d, J=0.9 Hz, 1H), 7.25–7.33 (m, 8H, aromatic *H*), 7.42–7.48 (m, 2H, aromatic *H*). ^{13}C NMR (125 MHz): δ=18.2, 18.6, 32.5, 59.5, 66.5, 70.6, 72.4, 126.8, 127.98, 128.04, 128.3, 128.4, 135.7, 139.0, 161.4. GC-MS (70 eV); *m/z* (%): 307 (10.9, M^+), 290 (93.5), 278 (10.7), 248 (12.8), 208 (100.0), 191 (25.4), 165 (58.0), 105 (10.9), 77 (7.8). FTIR ($CHCl_3$, cm^{-1}): 2962, 2928, 1680, 1658, 1657, 1602, 1447, 1262, 1098, 1010, 823. Anal. Calcd for $C_{20}H_{21}NO_2$: C 78.15, H 6.89, N 4.56. Found: C 78.33, H 7.37, N 4.55.

4.2.9. (1*S*,2*R*)-(−)-2-Chloro-*N*-(2-hydroxy-1-methyl-2-phenylethyl)acetamide (7a). White solid, mp 113–114°C (hexane). $[\alpha]_D$=−53.9 (*c* 1 $CHCl_3$). ^{1}H NMR (300 MHz) (as reported in Ref. 11). GC-MS (70 eV); *m/z* (rel.int.): 228 (0.5, M^++1), 210 (1.5), 134 (12.6), 121 (76.0), 107 (45.4), 86 (72.6), 77 (61.5), 57 (27.6), 44 (100.0). FTIR (KBr, cm^{-1}): 3308, 1646, (C═O), 1544 (NH), 1264, 1024, 760, 703, 585. Anal. Calcd for $C_{11}H_{14}NO_2Cl$: C 58.03, H 6.20, N 6.15. Found C 58.43, H 6.45, N 6.02.

4.2.10. (1*S*,2*S*)-(+)-2-Chloro-*N*-(2-hydroxy-1-methoxymethyl-2-phenylethyl)acetamide (7b). White solid, mp 114–116°C (Et_2O). $[\alpha]_D$=+43 (*c* 5.3 $CHCl_3$). ^{1}H NMR (300 MHz): δ 1.61 (br s, 1H, exchanges with D_2O), 3.37 (s, 3H, CH_3O), 3.39–3.49 (br s, 1H, which exchanges with D_2O), 3.54 and 3.59 (2×dd, 2H, AB part of an ABMX system, $^2J_{AB}$=9.6 Hz, $^3J_{AM}$=3.4 Hz, $^3J_{BM}$=4.0 Hz, CH_2O), 3.92 and 3.98 (2H, 2×d, AB system, $^2J_{AB}$=15.3 Hz, CH_2Cl), 4.14–4.21 (m, 1H, M part, C*H*NH), 5.04 (d, 1H, X part, $^3J_{MX}$=3.7 Hz, C*H*Ph), 7.25–7.35 (2m, 5H, aromatic *H*). ^{13}C NMR (APT, 50.3 MHz): δ 42.6 (*C*H_2Cl), 54.9 (*C*HNH), 59.4 (*C*H_3O), 73.5 (*C*H_2O), 74.3 (*C*HOH), 125.9 (Ar*C*H), 127.9 (Ar*C*H), 128.4 (Ar*C*H), 140.7 (Ar*C*), 166.3 (*C*ONH). GC-MS (70 eV); *m/z* (%): 240 (0.1, M^+−17), 121 (30.1), 119 (100.0), 84 (30.5), 79 (23.6), 77 (34.7), 74 (29.4). FTIR (KBr, cm^{-1}): 3320–3200 (br, OH), 1644 (C═O), 1527 (NH). Anal. Calcd for $C_{12}H_{16}NO_3Cl$: C 55.93, H 6.26, N 5.43. Found C 56.28, H 6.49, N 5.38.

4.2.11. (2*R*,1′*S*,2′*S*)-3,3-Diphenyl-*N*-(2-hydroxy-1-methoxymethyl-2-phenylethyl)oxiranecarboxamide (16a). White solid, mp 152–153°C (Et_2O). $[\alpha]_D$=+53.8 (*c* 0.5 $CHCl_3$). ^{1}H NMR (300 MHz): δ=2.00–2.20 (br s, 1H, exchanges with D_2O), 2.85 (dd, J=9.7 and 3.3 Hz, 1H), 3.14 (dd, J=9.7 and 3.8 Hz, 1H), 3.17 (s, 3H, CH_3O), 3.94 (s, 1H, C*H*C═O), 3.90–3.97 (m partially overlapping s at 3.94, 1H), 4.08 (d, J=7.6 Hz, 1H, C*H*OH), 6.41 (d, J=8.8 Hz, 1H, which exchanges slowly with D_2O), 7.07–7.54 (4m, 15H, aromatic *H*). ^{13}C NMR (50.3 MHz): δ=55.4, 59.0, 64.1, 67.6, 71.5, 74.6, 126.5, 127.9, 128.0, 128.4, 128.47, 128.51, 128.7, 129.0, 135.4, 138.6, 140.1, 167.2 (C═O). FTIR (KBr, cm^{-1}): 3415 (sharp), 3252 (broad), 3033, 1651 (C═O), 1529, 1494, 1448, 1124, 949, 704, 552. Anal. Calcd for $C_{25}H_{25}NO_4$: C 74.42, H 6.25, N 3.47. Found C 74.03, H 6.54, N 3.21.

4.2.12. (2*S*,1′*S*,2′*S*)-3,3-Diphenyl-*N*-(2-hydroxy-1-methoxymethyl-2-phenylethyl)oxiranecarboxamide (16b). White solid, mp 132–133°C (Et_2O). $[\alpha]_D$=+29.2 (*c* 1 $CHCl_3$). ^{1}H NMR (300 MHz): δ=2.30 (dd, J=9.4, 4.4 Hz, 1H), 2.83 (dd, J=9.4, 2.8 Hz, 1H), 3.00 (s, 3H, CH_3O), 3.20–3.40 (br s, 1H, exchanges with D_2O), 3.81 (s, 1H, C*H*C═O), 3.81–3.88 (m partially overlapping s at 3.81, 1H), 4.81 (d, J=4.8 Hz, 1H, C*H*OH), 6.51 (d, J=8.9 Hz, 1H, exchanges slowly with D_2O), 7.21–7.52 (3m, 15H, aromatic *H*). ^{13}C NMR (125 MHz): δ=53.6, 58.8, 63.7, 67.2, 72.1, 74.0, 126.1, 126.3, 127.7, 128.1, 128.29, 128.33, 128.4, 135.5, 138.6, 140.8, 166.7 (C═O). FTIR (KBr, cm^{-1}): 3457 (broad), 3417 (sharp), 3062, 2980, 1653 (C═O), 1536, 1450, 1122, 1050, 761, 629. Anal. Calcd for $C_{25}H_{25}NO_4$: C 74.42, H 6.25, N 3.47. Found C 74.15, H 6.47, N 3.24.

4.2.13. General procedure for the lithiation of the chloromethyloxazolines 8 and 12 and reaction with Ph_2CO in various solvents (Tables 1 and 2). A solution of LDA (1.4 equiv.) in the given solvent (1.6 mL $mmol^{-1}$) was cooled to −100°C with a methanol–liquid nitrogen bath. A mixture of oxazoline **8** or **12** (1 equiv.) and Ph_2CO (1.3 equiv.) in the given solvent (1.6 mL $mmol^{-1}$) was added dropwise and the resulting solution stirred at −100°C for the fixed time (see Tables 1 and 2) under N_2. Then, the reaction mixture was quenched with sat. aq. NH_4Cl and extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The resulting crude mixture of chlorohydrins **10a** and **10b** or **14a** and **14b** was purified by column chromatography (silica gel; petroleum ether/AcOEt 9:1) (see Tables 1 and 2 for isolated yields) and subsequently cyclized quantitatively to a diastereomeric mixture of epoxides **11a** and **11b** or **15a** and **15b** with NaOH/*i*-PrOH.[32] Diastereomers **11a** and **11b** could be separated and characterized as previously described. These new compounds showed the following data:

(2S,4′S,5′S)-2-(3,3-diphenyloxiranyl)-4-methoxymethyl-5-phenyl-2-oxazoline (major) (**15a**): Inseparable mixture of diastereomers (1.35–2:1 ratio by ^{1}H NMR analysis). Oil, see Table 2 for isolated yields in various solvents. ^{1}H NMR (500 MHz): δ=3.13 (dd, J=6.8, 9.7 Hz, 1H, CH_aOCH$_3$ minor), 3.30 (s, 3H, CH_3O minor), 3.36 (s, 3H, CH_3O major), 3.41–3.44 (m, 2H, CH_bOCH$_3$ minor+CH_aOCH$_3$ major), 3.52 (dd, J=4.3, 9.7 Hz, 1H, CH_bOCH$_3$ major), 3.94–4.01 (2m, 2H, C*H*CH$_2$ major+C*H*CH$_2$ minor), 4.19 (s, 1H, C*H* epoxide major), 4.23 (s, 1H, C*H* epoxide minor), 5.06 (d, J=7.5 Hz, 1H, C*H*Ph major), 5.19 (d, J=7.7 Hz, 1H, C*H*Ph minor), 6.70–6.72 (m, 2H, aromatic *H* minor), 6.92–6.94 (m, 2H, aromatic *H* major), 7.19–7.39 (3m, 22H, 11 aromatic *H* minor+11 aromatic *H* major), 7.51–7.57 (m, 4H, 2 aromatic *H* major+2 aromatic *H* minor). ^{13}C NMR (125 MHz): δ=59.0, 59.07, 59.13, 59.4, 66.61, 66.63, 73.6, 73.7, 74.0, 74.1, 84.0, 84.3, 125.2, 125.8, 126.7, 127.1, 127.81, 127.84, 128.02, 128.05, 128.14, 128.18, 128.28, 128.32, 128.35, 128.4, 128.5, 135.5, 135.6, 138.78, 138.84, 139.5, 139.6, 161.9, 162.2. GC-MS (70 eV) (major); *m/z* (%): 385 (3.4, M^+), 368 (9.1), 238 (35.6), 208 (36.7), 165 (82.1), 148 (100.0), 147 (99.5), 105 (42.1), 77 (27.2), 45 (56.9). GC-MS (70 eV) (minor); *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). FTIR (film, cm^{-1}) (major+minor): 3061, 2926, 1660 (C═N), 1679 (C═N), 1603, 1495, 1435, 1449, 1200, 1127, 977, 912, 758, 699. Anal. Calcd for $C_{25}H_{25}NO_3$: C 77.90, H 6.01, N 3.63. Found: C 78.28, H 6.22, N 3.65.

4.2.14. (2*S*,4′*S*,5′*S*)-2-(3,3-Bis-*p*-chlorophenyloxiranyl)-4-methoxymethyl-5-phenyl-2-oxazoline (17a) (presumed configuration of major isomer, methods A and B, see Table 3). Inseparable mixture of diastereomers. Oil, see Table 3 for isolated yields and dr. ^{1}H NMR (300 MHz): δ=3.23 (dd, J=6.2, 9.7 Hz, 1H, CH_aOCH$_3$ minor), 3.30 (s, 3H, CH_3O minor), 3.36 (s, 3H, CH_3O major), 3.40–3.52 (m, 3H, CH_2OCH$_3$ major+CH_bOCH$_3$ minor), 3.94–4.03 (m, 2H, C*H*CH$_2$ major+C*H*CH$_2$), 4.13 (s, 1H, C*H* epoxide major), 4.18 (s, 1H, C*H* epoxide minor), 5.07 (d, J=7.4 Hz, 1H, C*H*Ph major), 5.18 (d, J=7.8 Hz, 1H, C*H*Ph minor), 6.67–6.71 (m, 2H, aromatic *H* minor), 6.86–6.90 (m, 2H, aromatic *H* major), 7.21–7.45 (2m, 22H, 11 aromatic *H* minor+11 aromatic *H* major). ^{13}C NMR (125 MHz): δ=59.10, 59.12, 59.15, 59.4, 65.5, 65.6, 73.3, 73.5, 74.0, 74.1, 76.7, 125.2, 125.8, 128.08, 128.11, 128.2, 128.38, 128.43, 128.49, 128.52, 128.58, 128.65, 128.7, 129.47, 129.55, 133.64, 133.65, 134.31, 134.34, 134.5, 134.6, 136.81, 136.83, 139.1, 139.4, 161.4, 161.6. GC-MS (70 eV) (major); *m*/*z* (%): 455 (0.8, M$^+$+2), 453 (1.0, M$^+$), 438 (7.9), 436 (9.7), 199 (21.6), 148 (100.0), 116 (28.7), 91 (19.5), 45 (53.0). GC-MS (70 eV) (minor); *m*/*z* (%): 453 (0.7, M$^+$), 438 (3.9), 436 (5.8), 199 (23.7), 148 (100.0), 116 (29.2), 91 (11.9), 45 (46.9). FTIR (film, cm^{-1}) (major+minor): 3034, 2926, 1668 (C=N), 1598, 1491, 1400, 1322, 1201, 1198, 1091, 1015, 974, 822, 698.

4.2.15. (2*S*,4′*S*,5′*S*)-2-(1-Oxaspiro[2,5]ottanyl)-4-methoxymethyl-5-phenyl-2-oxazoline (17b) (presumed configuration of the major isomer according to Barbier's technique, see Table 3). Inseparable mixture of diastereomers. Oil, see Table 3 for isolated yields and dr. ^{1}H NMR (500 MHz): δ 1.44–1.66 (2m, 12H, 6 cyclohexyl *H* major+6 cyclohexyl *H* minor), 1.70–1.82 (m, 8H, 4 cyclohexyl *H* major+4 cyclohexyl *H* minor), 3.36 (s, 3H, CH_3O major), 3.37 (s, 3H, CH_3O minor), 3.46 (s, 1H, C*H* epoxide major), 3.47 (d, J=1.1 Hz, 1H, C*H* epoxide minor), 3.48–3.52 (m, 2H, CH_aOCH$_3$ major+CH_aOCH$_3$ minor), 3.58–3.63 (m, 2H, CH_bOCH$_3$ major+CH_bOCH$_3$ minor), 4.15–4.21 (m, 2H, C*H*CH$_2$ major+C*H*CH$_2$ minor), 5.34 (d, J=7.0 Hz, 1H, C*H*Ph major), 5.36 (d, J=6.9 Hz, 1H, C*H*Ph minor), 7.24–7.36 (2m, 10H, 5 aromatic *H* major+5 aromatic *H* minor). GC-MS (70 eV) (major); *m*/*z* (%): 301 (6.3, M$^+$), 284 (20.1), 256 (29.7), 228 (15.7), 200 (20.7), 148 (76.2), 116 (64.8), 105 (24.8), 91 (38.8), 81 (39.4), 67 (100.0), 45 (39.2). GC-MS (70 eV) (minor); *m*/*z* (%): 301 (20.5, M$^+$), 256 (38.5), 228 (19.1), 200 (23.4), 148 (99.8), 116 (70.5), 105 (27.5), 91 (42.2), 81 (42.5), 67 (100.0), 45 (77.43). FTIR (film, cm^{-1}) (major+minor): 3033, 2932, 1674 (C=N), 1448, 1270, 1193, 1127, 976, 735, 699.

4.2.16. (2*S*,4′*S*,5′*S*)-2-(1-Oxaspiro[2,11]tetradecanyl)-4-methoxymethyl-5-phenyl-2-oxazoline (17c) (presumed configuration of the major isomer according to method B, see Table 3). Inseparable mixture of diastereomers. Waxy solid, see Table 3 for isolated yields and dr. ^{1}H NMR (500 MHz): δ=1.34 (br s, 28H, 14 cyclododecyl *H* major+14 cyclododecyl *H* minor), 1.50–1.60 (m, 10H, 5 cyclododecyl *H* major+5 cyclododecyl *H* minor), 1.61–1.71 (m, 4H, 2 cyclododecyl *H* major+2 cyclododecyl *H* minor), 1.81–1.86 (m, 2H, 1 cyclododecyl *H* major+1 cyclododecyl *H* minor), 3.35 (s, 3H, CH_3O major), 3.37 (s, 3H CH_3O minor), 3.44 (d, J=1.1 Hz, 1H, C*H* epoxide major), 3.45 (s, 1H, C*H* epoxide minor), 3.51 (dd, J=5.8, 9.7 Hz, 2H, CH_aOCH$_3$ major+CH_aOCH$_3$ minor), 3.58–3.63 (m, 2H, CH_bOCH$_3$ major+CH_bOCH$_3$ minor), 4.16–4.21 (m, 2H, C*H*CH$_2$ major+C*H*CH$_2$ minor), 5.35 (d, J=7.2 Hz, 1H, C*H*Ph major), 5.37 (d, J=7.0 Hz, 1H, C*H*Ph minor), 7.24–7.35 (2m, 10H, 5 aromatic *H* major+5 aromatic *H* minor). GC-MS (70 eV) (major); *m*/*z* (%): 385 (5.0, M$^+$), 368 (7.3), 340 (17.7), 312 (10.5), 238 (61.9), 205 (22.1), 148 (100.0), 118 (19.1), 116 (34.4), 91 (24.3), 83 (12.0), 77 (10.0), 67 (33.2), 55 (41.1), 45 (57.2), 41 (38.6). GC-MS (70 eV) (minor); *m*/*z* (%): 385 (5.2, M$^+$), 368 (8.1), 340 (22.9), 312 (10.6), 238 (57.4), 205 (21.7), 148 (100.0), 116 (36.3), 105 (14.6), 91 (24.2), 77 (11.0), 67 (39.3), 55 (48.7), 45 (68.0), 41 (50.2). FTIR (KBr, cm^{-1}) (major+minor): ν=2930, 1651 (C=N), 1474, 1326, 1131, 1084, 961, 745, 700.

4.2.17. (3*R*,4′*S*,5′*S*)-2-(Adamantane-2-spiro-2′-oxiranyl)-4-methoxymethyl-5-phenyl-2-oxazoline (17d) (presumed configuration of the major isomer according to Barbier's technique, see Table 3). Inseparable mixture of diastereomers. Oil, see Table 3 for isolated yields and dr. ^{1}H NMR (500 MHz): δ=1.43–2.06 (3m, 28H, 14 adamantyl *H* major+14 adamantyl *H* minor), 3.33 (s, 3H, CH_3O minor), 3.35 (s, 3H, CH_3O major), 3.43–3.45 (m overlaps singlets at 3.48 and 3.49, 2H, CH_aOCH$_3$ major+CH_aOCH$_3$ minor), 3.48 (s, 1H, C*H* epoxide major), 3.49 (s, 1H, C*H* epoxide minor), 3.56–3.62 (m, 2H, CH_bOCH$_3$ major+CH_bOCH$_3$ minor), 4.10–4.18 (m, 2H, C*H*CH$_2$ major+C*H*CH$_2$ minor), 5.32 (d, J=6.9 Hz, 1H, C*H*Ph minor), 5.34 (d, J=6.9 Hz, 1H, C*H*Ph major), 7.23–7.33 (2m, 10H, 5 aromatic H major+5 aromatic H minor). ^{13}C NMR (125 MHz): δ=26.70, 26.73, 26.85, 26.88, 30.7, 30.9, 34.93, 34.97, 34.99, 36.1, 36.52, 36.55, 36.6, 36.9, 37.0, 57.2, 57.3, 59.0, 59.1, 70.2, 70.5, 73.66, 73.73, 74.08, 74.12, 83.9, 84.0, 125.60, 125.61, 128.1, 128.2, 128.57, 128.59, 140.04, 140.06, 163.28, 163.29. GC-MS (70 eV) (major); *m*/*z* (%): 353 (2.9, M$^+$), 336 (65.7), 308.10 (22.0), 252 (24.9), 206 (55.8), 148 (100.0), 116 (45.1), 105 (28.8), 91 (62.0), 77 (34.6), 67 (30.6), 45 (56.3). GC-MS (70 eV) (minor); *m*/*z* (%): 353 (1.29, M$^+$), 336 (27.98), 304 (8.77), 252 (10.17), 206 (45.32), 148 (100), 116 (38.36), 105 (19.04), 91 (48.29), 77 (22.55), 67 (24.28), 45 (62.46). FTIR (film, cm^{-1}) (major+minor): ν=3413, 2910, 1674 (C=N), 1450, 1195, 1128, 981, 699.

X-Ray crystallographic data[33] (excluding structure factors) for **4a**, **10a** and **16a** have been deposited at the Cambridge Crystallographic Data Centre.[34]

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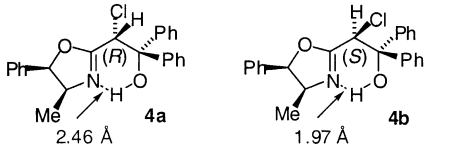
References

1. Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **1996**, *37*, 4781–4784.
2. Scheeren, J. W.; Lange, J. *Tetrahedron Lett.* **1984**, *25*, 1609–1612.
3. Evans, D. A.; Williams, J. M. *Tetrahedron Lett.* **1988**, *29*, 5065–5068.
4. (a) Takeda, Y.; Matsumoto, T.; Sato, F. *J. Org. Chem.* **1986**, *51*, 4728–4731. (b) Howe, G. P.; Wang, S.; Procter, G. *Tetrahedron Lett.* **1987**, *28*, 2629–2632.
5. Molander, J. A.; Shubert, D. C. *J. Am. Chem. Soc.* **1987**, *109*, 576–578.
6. Parikh, J. R.; Doering, W.vonE. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
7. Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165–185.
8. Preliminary results presented at 5th International Symposium on Carbanion Chemistry, Sendai, Japan, August 1-4, 1998, PP 007, p 91.
9. Breton, P.; Andrè-Barres, C.; Langlois, Y. *Synth. Commun.* **1992**, *22*, 2543–2554.
10. Oxazoline **1a** was prepared by the reaction of (1*R*,2*S*)-(−)-norephedrine with ethyl acetimidate hydrochloride according to a procedure reported by: (a) Meyers, A. I.; Knaus, G.; Kamata, K.; Ford, M. E. *J. Am. Chem. Soc.* **1976**, *98*, 567–576. Compound **1a** showed an optical activity ($[\alpha]_D=-246$, *c* 1 $CHCl_3$) quite close to that recently reported by: (b) Kamata, K.; Agata, I.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 3113–3116.
11. Mintz, M.J.; Walling, C. *Organic Syntheses*; Wiley & Sons: New York, 1973; Collect. Vol. V, pp 184–187. One equiv. of *tert*-butyl hypochlorite has to be used. An excess causes the undesired formation of 2,2-dichloromethyl-4-methyl-5-phenyl-2-oxazoline. While this paper was in preparation, a paper on the synthesis of chiral chloromethyloxazolines has been published: Kamata, K.; Sato, H.; Takagi, E.; Agata, I.; Meyers, A.I. *Heterocycles* **1999**, *51* (2), 373–378.
12. Attempted further purification of **2** by distillation caused decomposition and prolonged contact with silica gel promoted ring opening to give the hydroxy amide **7a** (Chart 1). Belvisi, L.; Gennari, C.; Poli, G.; Scolastico, C.; Salom, B.; Vassallo, M. *Tetrahedron* **1992**, *48*, 3945–3960.
13. PM3 calculations (Ref. 14) have confirmed the existence in compound **4b** of a favored intramolecular hydrogen bonding involving the hydroxy group and the oxazolinyl nitrogen atom (Chart 1). Some of the different geometries used as starting structures have led to hydrogen-unbonded higher energy minima ($+3.0$ kcal mol^{-1}). The latter present additional destabilizing interactions between the oxazolinyl ring and one of the phenyl groups α to OH. The distance between the phenyl and the oxazolinyl ring is less than 2 Å, to be compared with a distance of more than 3.4 Å in the hydrogen-bonded conformation. Therefore, the hydrogen bond conformation allows an ideal arrangement of the rings, minimizing steric interactions. Both stabilizing factors sinergically contribute to determine the most favored geometry of **4b** (Chart 1). Similar results were obtained for the diastereoisomer **4a**. In this case, the hydrogen bond is somewhat longer due to an optimal reciprocal arrangement of the three phenyl rings (Chart 1). It is worth pointing out that the X-ray analysis of **4a** showed a lower value of the N–HO bond distance (1.97 Å). This must be ascribed to the known underestimation of non-bonding forces by semiempirical calculations. (Ref. 22).
14. MOPAC 6.0: Stewart, J. J. P. *QCPE* **1990**, *455*. All of the calculations were performed using the PM3 Hamiltonian, with the keywords PM3, EF, and PRECISE in order to meet rigorous criteria. Geometries were optimized with no symmetry constraints.
15. Evidences have been reported for lithium azaenolates derived from 2-ethyl-4-methoxymethyl-5-phenyl-2-oxazoline: (a) Hobbler, M. A.; Bergbreiter, D. E.; Newcomb, M. *J. Am. Chem. Soc.* **1978**, *100*, 8182–8185. (b) Meyers, A. I.; Snyder, E. S.; Ackerman, J. J. H. *J. Am. Chem. Soc.* **1978**, *100*, 8186–8189. (c) Le Bail, M.; Aitken, D. J.; Vergne, F.; Husson, H. P. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1681–1689.
16. A multinuclear investigation in THF at low temperature combined with a study of chemical shift/charge relationships and semiempirical calculations on the lithium salt of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline had provided structural insights into the nature of this anionic system. In particular, semiempirical calculations had indicated that, of the two possible geometrical isomers, the *E* one is the more stable, as a result of an internal chelation involving the chlorine atom. See: Abbotto, A.; Bradamante, S.; Florio, S.; Capriati, V. *J. Org. Chem.* **1997**, *62*, 8937–8940.
17. Meyers, A. I.; Yamamoto, Y.; Mihelich, E. D.; Bell, R. A. *J. Org. Chem.* **1980**, *45*, 2792–2796.
18. Oxazoline **8** has been prepared by chlorination (analogously to the preparation of **2** and **12**) of the corresponding (4*S*)-4-isopropyl-2-methyl-2-oxazoline **1b**, which was synthesized by condensation of L-2-amino-3-methyl-1-butanol with ethyl acetimidate hydrochloride as reported: Kurth, M. J.; Decker, O. H. W. *J. Org. Chem.* **1985**, *50*, 5769–5775.
19. Less advantageously compound **12** can be prepared from 3-methoxy-2-amino-1-phenyl propanol and the ethyl imidate of chloroacetonitrile. See: Meyers, A. I.; Knaus, G.; Kendall, P. M. *Tetrahedron Lett.* **1974**, *39*, 3495–3498. (4*S*,5*S*)-(−)-2-methyl-4-methoxymethyl-5-phenyl-2-oxazoline can also be prepared as reported in Ref. 10a,b.
20. Structure and energetics of intermediate lithium azaenolates have been computationally investigated at semiempirical



PM3 computed N-H bond distance of compounds **4a** and **4b**

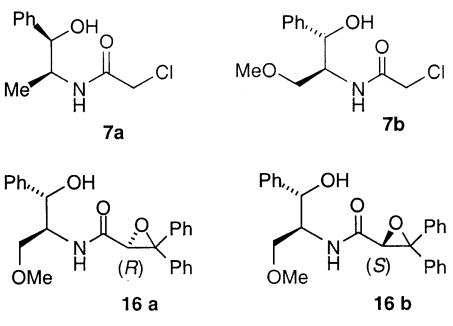


Chart 1.

(Refs. 14,21,22) and ab initio (Ref. 23) level. In order to correctly account for weak intramolecular (intramolecular coordination) and intermolecular (coordination with molecules of solvent) bond forces it is necessary to include electron correlation. We have applied in the present work the semiempirical PM3 Hamiltonian and the Density Functional Theory (DFT) (Ref. 24) with the B3LYP functional (Ref. 25). It has been shown that the semiempirical PM3 approach is adequate to correctly compute geometries, whereas it may have large errors in the energy calculations (Ref. 22). For the above reason, geometries were fully optimized at semiempirical level but corresponding energies have been compared with ab initio level (DFT//PM3) computations.

21. PM3 lithium parameters: Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301–1312.
22. The PM3 semiempirical Hamiltonian has been recently shown to well compare with high level electron-correlated ab initio computations performed on lithium enolates: Abbotto, A.; Streitwieser, A.; Schleyer, P. V. R. *J. Am. Chem. Soc.* **1997**, *119*, 11255–11268, and referenced cited therein.
23. All ab initio calculations used the GAUSSIAN 94 program package: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. *Gaussian 94*, Revision E.2; Gaussian, Inc.: Pittsburgh PA, 1995.
24. Seminario, J. M., Politzer, P., Eds.; Modern Density Functional Theory. A Tool for Chemistry, Elsevier: New York, 1995; Vol. 2.
25. (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785–789.
26. The bridged structure, where the charge on the cation is stabilized by a π-interaction with the azaenolate anion, has been often found as a particularly stable species, as in the case of lithium enolates (Ref. 22) or aromatic alkyllithium derivatives (Anders, E.; Opitz, A.; van Eikema Hommes, N. J. R.; Hampel, F. *J. Org. Chem.* **1993**, *58*, 4424–4430).
27. We took into account the role of this effect by explicitly including two molecules of solvent[22] in the PM3 geometry optimization and energy calculation of the lithium azaenolate **9**. As a model of ethereal solvent we chose dimethyl ether.
28. Charges on lithium are +0.32 and +0.21 for (*E*)-**13a** and (*E*)-**13b**, respectively. In the methoxy group, charges on the oxygen atoms are −0.27 and −0.18, respectively.
29. Meyers had reported that in lithiated 2-ethyl-4-methoxymethyl-5-phenyloxazoline the methoxy group provides coordination to lithium thus determining the stereochemistry of the reaction with electrophiles. Meyers, A. I. *Acc. Chem. Res.* **1978**, *11*, 375–381. The authors did not mention any coordination of lithium cation by chlorine in 2-lithiochloromethyl-4-methoxymethyl-5-phenyl-2-oxazoline. See Ref. 19.
30. Three preliminary communications on highly diastereoselective aldol-type reactions via differently substituted boron and titanium azaenolates of chiral oxazolines with ketones and aldehydes, have been recently reported: (a) Florio, S.; Capriati, V.; Luisi, R.; Abbotto, A. *Tetrahedron Lett.* **1999**, *40*, 7421–7425. (b) Florio, S.; Capriati, V.; Luisi, R. *Tetrahedron Lett.* **2000**, *41*, 5295–5298. (c) Capriati, V.; Florio, S.; Luisi, R. *Eur. J. Org. Chem.* **2001**, 2035–2039.
31. Suffert, J. *J. Org. Chem.* **1989**, *54*, 509–512.
32. Florio, S.; Capriati, V.; Russo, V. *Gazz. Chim. Ital.* **1997**, *127*, 587–595.
33. The Bruker X-ray structure refinement package consists of SAINT Version 5, SHELXTL Version 5, and SMART Version 5 and is marketed by Bruker AXS, Inc., Madison, WI.
34. Deposition number CCDC-124102 for compound **4a**, CCDC 124100 for compound **10a** and CCDC-124101 for compound **16a**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (internat.) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk).