On the Addition of Lithiated 2-Alkyl- and 2-(Chloroalkyl)-4,5-dihydro-1,3-oxazoles to Nitrones − A Mechanistic Investigation

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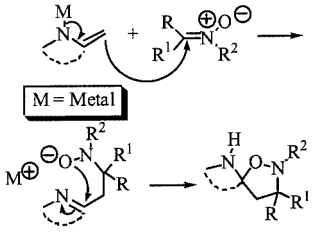
The addition of 2-(lithioalkyl)-4,5-dihydro-1,3-oxazoles **2a–c** and 2-[chloro(lithio)alkyl]-4,5-dihydro-1,3-oxazoles **2d**,**e** to nitrones **3** has been studied. While lithiated 2-methyl-4,5-dihydro-1,3-oxazole **2a** adds stereoselectively to nitrones **3**, resulting after long reaction times (3 h) in the formation of 2-[(*E*)-alkenyl]-4,5-dihydro-1,3-oxazoles **8a–h**, lithiated 2-(chloromethyl)-4,5-dihydro-1,3-oxazole **2e** affords 2-[(*Z*)-alkenyl]-4,5-dihydro-1,3-oxazoles **26a–d** and **26f–h**. α-Lithiated 2-ethyl-4,5-dihydro-1,3-oxazole **2b** adds to **3a** to give the 1,6-dioxa-2,9-diazaspiro[4.4]nonane **9** and 2-alkenyl-4,5-dihydro-1,3-oxazole **14** after treatment with oxalic acid. Quenching after short reaction times shows that the conversions of **2a** to **8** and of **2b** to **14** go through spirocyclic compounds **7** and **9**, while the reaction between **2e** and **3a**, quenched even at short reaction times, gives a mixture of the 1,6-dioxa-2,9-diazaspiro[4.4]nonanes **21-H** and **22-H** and the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazoles **25a** and **27a**. The addition of **2c** to **3a** furnishes the 1,6-dioxa-2,9-diazaspiro[4.4]nonane **15** and then isoxazolidin-5-one **16** upon hydrolysis with oxalic acid. The addition of **2d** to **3a** gives the 1,6-dioxa-2,9-diazaspiro[4.4]nonanes **17b** and **18b** after short reaction times and the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **19** after long reaction times.

Introduction

Nucleophilic addition of carbon nucleophiles, including enolates, to nitrones has been extensively investigated in recent years.[1] Nucleophilic addition of azaenolates to nitrones, which would be expected to produce *N*-(3-iminoalkyl)hydroxylamines or, in the case of cyclic azaenolates, spirocyclic isoxazolidines, has not been studied so far (Scheme 1).[2]



Scheme 1

In our research work concerning the chemistry of metallated 2-alkyl-4,5-dihydro-1,3-oxazoles with electrophiles,[3] we have recently discovered[4] that lithiated 2-(chloromethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole and 2,4,4-trimethyl-4,5-dihydro-1,3-oxazole react highly stereoselectively with a number of nitrones to give 2-[(*Z*)- and (*E*)-alkenyl]-4,5-dihydro-1,3-oxazoles. In order to explain the stereoselectivity of the above reactions and to obtain mechanistic information we decided to study the addition of such lithiated species to nitrones in some detail, and we report the relevant results here.

Results and Discussion

2-(Lithiomethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**2a**), generated by deprotonation of 2,4,4-trimethyl-4,5-dihydro-1,3-oxazole (**1a**) (LDA, THF, −98 °C) (Scheme 2), probably exists in equilibrium between an imine and an enamine form, as suggested by certain spectroscopic evidence obtained for lithiated 2-alkyl-4,5-dihydro-1,3-oxazoles.[5] We found that the addition of the commercially available nitrone **3a** to the lithiated species **2a**, followed by immediate (a few seconds) quenching with sat. aq. NH_4Cl, afforded a high yield (78%) of the crystalline hydroxylamino derivative **6**.[6] Compound **6**, the structure of which has been established spectroscopically (^1H and ^{13}C NMR, MS-ESI, IR, and elemental analysis), is probably the result of the nucleophilic addition of **2a** to **3a**, yielding the lithiated hydroxylamine **4**, which then cyclizes on the C=N bond of the 4,5-dihydro-1,3-oxazole moiety to give the spirocyclic form **5**. Acidic quenching would produce the hydroxylamine derivative **6**, which, when in $CDCl_3$ solution, equilibrates with the spirocyclic compound **7** (two diastereomers) [**7**/**6** = 7.1:1; *dr*(**7**) = 7:3] (Scheme 2).

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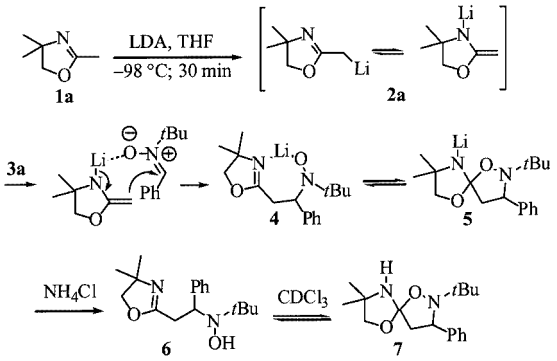
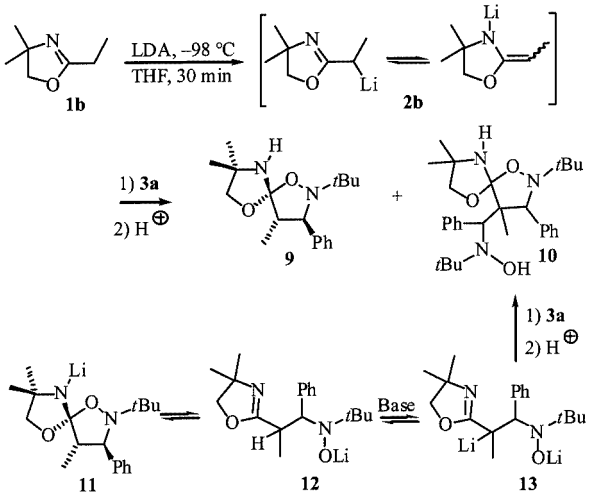


Scheme 2

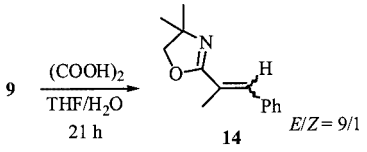
Quenching of the reaction mixture obtained by addition of nitrone **3a** to **2a** with satd. aq. NH_4Cl after 18 h gave the 2-[(*E*)-styryl]-4,5-dihydro-1,3-oxazole **8a** (Table 1) in excellent yield (95%) and diastereomeric ratio [(*E*)/(*Z*) > 99:1; $^3J_{H,H(E)}$ = 15.8 Hz]. A high (*E*) stereoselectivity was also observed in the reaction with other aryl or alkyl nitrones **3b**−**h**, providing the corresponding 2-[(*E*)-alkenyl]-4,5-dihydro-1,3-oxazoles **8b**−**h** in good yields (Table 1). The *anti*-β elimination of *tert*-butylhydroxylamine occurring in compound **6** could be the stereoselective determining step, as previously reported.[4]

Lithiation of commercially available 2-ethyl-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**1b**) to give 2-(1-lithioethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**2b**), followed by the addition of nitrone **3a**, gave rise (after 3 h) to the formation of the 1,6-dioxa-2,9-diazaspiro[4.4]nonane **9** (70% yield) as a mixture of three diastereoisomers (*dr* = 87:9:4) (structures ascertained by NOESY phase-sensitive experiments) and a very small amount of **10** (ca. 2% yield) (Scheme 3). A possible explanation for the formation of **10** is also shown in Scheme 3. Lithiated spirocyclic compound **11**, present in the reaction mixture, opens to give **12**, which would undergo further deprotonation to generate the dilithiated species **13**. Treatment with nitrone **3a**, cyclization, and acidic quenching would furnish **10**. In comparison with **4**, compound **12**, which probably equilibrates with its spirocyclic form **11** in solution, is much less prone to eliminate *tert*-butylhydroxylamine, under the basic conditions of the reaction mixture, for steric reasons due to the methyl substitution and for having only one hydrogen atom β to the lithiated hydroxylamine group.



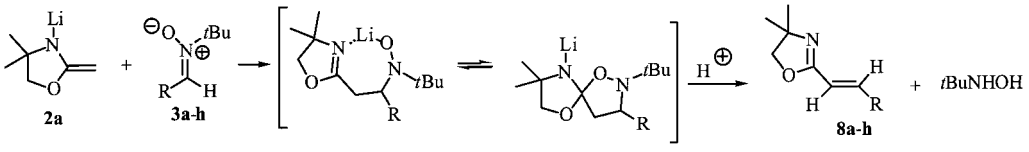
Scheme 3

However, treatment of the isolated spirocyclic compound **9** with 1 equiv. of oxalic acid gave a quantitative yield of the 4,4-dimethyl-2-(1-methyl-2-phenylvinyl)-4,5-dihydro-1,3-oxazole (**14**) [diastereomeric mixture: (*E*)/(*Z*) = 9:1]. Diastereomers could be separated by column chromatography[7] (Scheme 4).



Scheme 4

Table 1. Synthesis of 2-[(*E*)-alkenyl]-4,5-dihydro-1,3-oxazoles **8**

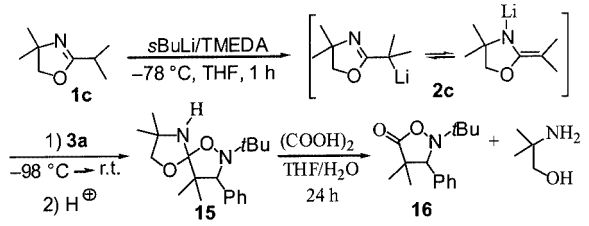


Nitrone	R	Compound (yield %)[a][b]	Conversion (%)	(*E*)/(*Z*)[c]
3a	Ph	**8a** (95)	> 95	> 99:1
3b	*p*-MeC_6H_4	**8b** (95)	> 95	> 99:1
3c	*p*-ClC_6H_4	**8c** (70)	> 95	> 99:1
3d	*p*-$CH_3OC_6H_4$	**8d** (85)	90	> 99:1
3e	2,4,6-$(CH_3O)_3C_6H_2$	**8e** (95)	70	> 99:1
3f	3,4-(methylenedioxy)C_6H_3	**8f** (70)	> 95	> 99:1
3g	cyclohexyl	**8g** (60)	> 95	> 99:1
3h	$CH_3[CH_2]_6$	**8h** (52)	> 95	> 99:1
3i	*p*-$O_2NC_6H_4$	**8i**[d]	–	–

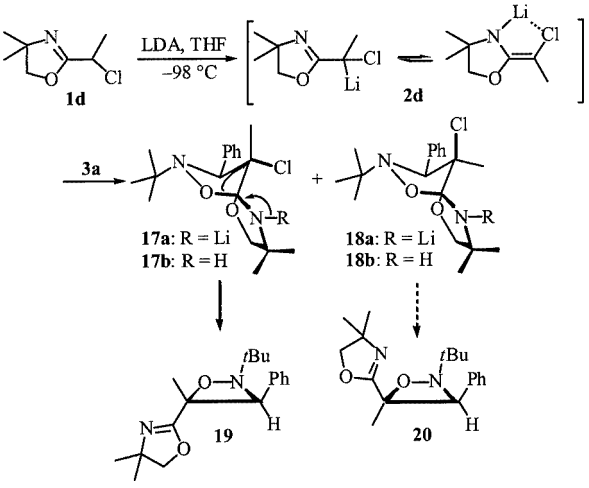
[a] Based on the converted nitrone. [b] Yields were not optimized. [c] Determined by ^1H NMR analysis. [d] No reaction.

2-(1-Lithio-1-methylethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**2c**), readily available from **1c**,[8] added to nitrone **3a** to furnish the 1,6-dioxa-2,9-diazaspiro[4.4]nonane **15** (*dr* = 95:5 by ^{1}H NMR, 69% yield). Compound **15** could be hydrolyzed into the corresponding isoxazolidin-5-one **16** (73% yield, conv. 73%) with oxalic acid (Scheme 5). Compound **15**, of course, having no β-hydrogen atom, could not eliminate *tert*-butylhydroxylamine. The conversion of spirocyclic compound **15** into the isoxazolidin-5-one **16** occurs very easily. In comparison, compound **9** does not undergo this kind of reaction, the β-elimination of hydroxylamine to give the alkene **14** evidently being faster.

Treatment of 2-(1-chloro-1-lithioethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**2d**)[9] with **3a** (Scheme 6) furnished the spirocyclic compounds **17b** and **18b** and the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **19** in relative amounts that depended upon the reaction times. Quenching of the reaction mixture after a very short reaction time (5 s) yielded 80% of **17b** and **18b** (**17b**/**18b** = 13:1) and 20% of **19**, while quenching after 10 min afforded 57% of **17b** and **18b** (**17b**/**18b** = 5:1) and 39% of **19**. Finally, quenching performed after 1 h gave 85% of **19** and a small amount (< 5%) of **17b** and **18b** (Scheme 6).[10] All these data seem to suggest that lithiated spirocyclic compound **17a** tends to convert into the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **19**, through a stereoelectronically allowed ring-contraction process. Here the NLi group would provide the electronic "push" to form the dihydrooxazolyl ring, and the isoxazolidine ring would contract by oxygen migration and chloride replacement. If we look at the orbitals involved in the reaction, we can understand why this ring-contraction



Scheme 5

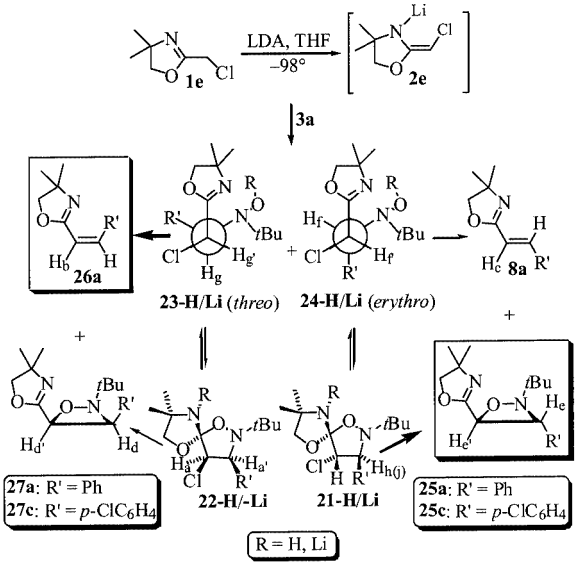


Scheme 6

takes place. As the Cl leaving group departs, electrons in the σ bond to the migrating group (oxygen atom) have to flow into the C−Cl σ* orbital. The best overlap between these two orbitals (σ and σ*) occurs when they are oriented *anti*-periplanar to one another (Scheme 6). Such an *anti*-periplanar requirement is not permitted for **18a**, which does not convert into the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **20**. In an experiment designed to test the above considerations, the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **19** was formed quantitatively when a sample of **17b** was treated with 1 equiv. of LDA in THF (−98 °C, THF). Under the same conditions, the spirocyclic compound **18b** did not transform into the oxazetidine **20** and was quantitatively recovered unchanged. The relative configurations of compounds **17b** and **18b** were assigned by means of NOESY phase-sensitive experiments[11] and confirmed by an X-ray analysis (see Supporting Information), while the relative configuration of the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **19** was determined by the NOESY phase-sensitive spectrum and confirmed by ^{1}H NMR correlation with spectroscopic data of the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazoles **25a** and **27a** (see below).[12]

The reaction between lithiated 2-(chloromethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole **2e** and nitrone **3a** was carefully investigated. We found that addition of **2e** to **3a** and acidic quenching after 3 h gave alkenes **26a** and **8a** (46% yield; **26a**/**8a** = 97:3), together with the 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazoles **25a** (22% yield) and **27a** (7% yield) (Scheme 7, Figure 1). In order to explain the formation of the above alkenes and oxazetidines, a careful examination of the reaction mixture at shorter reaction times, supported by ^{1}H NMR investigation, was performed. The reaction mixture obtained by addition of **3a** to **2e**[3a,13] (Scheme 7, Figure 1) with quenching after 1 min was chromatographed to give the *trans*-spirocyclic compound **21-H** (7%), a mixture of the *threo*/*erythro* (4.1:1 ratio) compounds **23-H** and **24-H** and the *cis*-spirocyclic compound **22-H** (44% combined yield; (**23-H** + **24-H**)/**21-H** = 9:1), *trans*-2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **25a** (2%), *cis*-2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **27a** (1%), and a mixture of the two 2-[(*Z*)- and (*E*)-alkenyl]-4,5-dihydro-1,3-oxazoles **26a** and **8a** [13% combined yield; (*Z*)/(*E*) = 3:1]. All these compounds were isolated and spectroscopically characterized. ^{1}H NMR inspection of the above reaction mixture after 1 min (Figure 1) showed the presence of a diastereomeric mixture of two *trans*-1,6-dioxa-2,9-diazaspiro[4.4]nonanes **21-H**,[14] together with the *cis*-spirocyclic form **22-H** [**22-H**/**21-H** = 7:3; *dr*(**21-H**) = 6:1], a diastereomeric mixture of the corresponding hydroxylamine forms **23-H** and **24-H** (*threo*/*erythro* = 4.1:1),[15] a mixture of *cis*- and *trans*-2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazole **27a** and **25a**[13] (*cis*/*trans* = 1:2), and a mixture of (*Z*)- and (*E*)-4,4-dimethyl-2-styryl-4,5-dihydro-1,3-oxazoles **26a** and **8a** [(*Z*)/(*E*) = 3:1]. ^{1}H NMR inspection after longer reaction times (Figure 1) revealed that signals corresponding to the 4,5-dihydro-1,3-oxazole **25a**, as well as to (*Z*)-alkene derivative **26a**, tended to increase while signals of spirocyclic compounds **21-H** and **22-H** and the correspond-

ing opened forms **24-H** and **23-H** tended to decrease. According to these results it is reasonable that the stereoselective determining step in the reaction between **2e** and nitrone **3a** is the addition of the litiated species **2e** to the C=N bond of **3a**. Now, the point is: why are (*Z*)-alkene **26a** and *trans*-4,5-dihydro-1,3-oxazole **25a** the main reaction products at long reaction times? In view of the fact that oxazetidines could derive primarily from a ring-contraction process of the spirocyclic compounds (as just seen for **17b** and **18b**) and that the molar ratio between the opened forms **23-H** and **24-H** and the corresponding spirocyclic compounds **21-H** and **22-H** is approximately constant during the reaction (4:1 and 3:1, respectively), it is possible that the conversion of **21-Li** into **25a** could be more favored than that of **22-Li** to **27a** for the same reason as why **17b** affords **19** but **18b** does not give **20**. It follows that the propensity of **21-Li** and **23-Li** to give **25a** and **26a** could be higher than that of **24-Li** and **22-Li** to give **8a** and **27a**, respectively, which would explain the increasing amounts of **25a** and **26a** with time.



Scheme 7

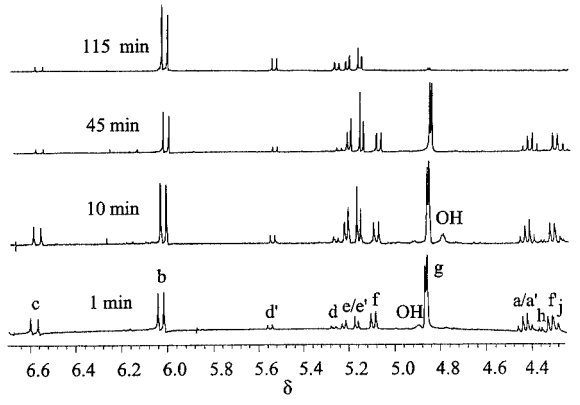


Figure 1. Time-resolved ^{1}H NMR (500 MHz) spectra for the reaction between **2e** and **3a** in $CDCl_3$ at room temperature; the reaction time is marked on each spectrum

We have also established that the alkenes do not originate from oxazetidines. Indeed, subjection of a mixture of the *threo*/*erythro* forms of **23-H** and **24-H** (*threo*/*erythro* = 87:13) to deprotonation with 1 equiv. of LDA resulted after 2 h in the formation of a mixture of alkenes **26a** and **8a** [(*Z*)/(*E*) = 90:10] and oxazetidines **25a**/**27a** (*trans*/*cis* = 53:47). In contrast, starting from a mixture of the two *trans*-spirocyclic compounds **21-H**, only the *trans*-oxazetidine **25a** (87%) and traces of alkene **8a** formed upon treatment with 1 equiv. of LDA. Moreover, upon warming to high temperatures (300 °C) or treatment with NaH/DMSO, the *trans*-oxazetidine **25a** cycloreverted to a mixture of 4,5-dihydro-1,3-oxazole-2-carbaldehyde and *N*-*tert*-butylbenzylidenimine. Therefore, alkenes **26a** and **8a** cannot have been formed from oxazetidines **27a** and **25a**, respectively.

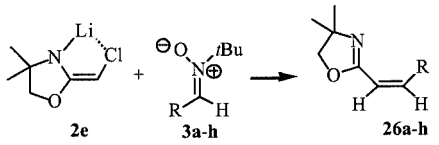
Treatment of **2e** with nitrones **3b**−**d** and **3f**−**h** with quenching after 3 h afforded the 2-[(*Z*)-alkenyl]-4,5-dihydro-1,3-oxazoles **26** (see Table 2) highly stereoselectively, with the (*Z*)/(*E*) ratios ranging from 90:10 to 97:3. In all cases, small amounts of the corresponding *cis*- and *trans*-oxazetidines were observed in the ^{1}H NMR spectra of the crude reaction mixtures. In the case of the reaction between **2e** and **3c**, oxazetidines **25c** and **27c** (Scheme 7) were also isolated and characterized.

Conclusion

In conclusion, we report in this paper that lithiated 2-alkyl-4,5-dihydro-1,3-oxazoles **2a**,**b** add highly stereoselectively to nitrones **3** to produce isolable 1,6-dioxa-2,9-diazaspiro[4.4]nonanes initially, and then 2-[(*E*)-alkenyl]-4,5-dihydro-1,3-oxazoles **8** and **14** at longer reaction times (3 h), with elimination of *tert*-butylhydroxylamine. The reaction between **2c** and **3a** ends with the formation of spirocyclic compound **15** (the hydroxylamine elimination not being possible).

The lithiated 2-(chloromethyl)- and 2-(1-chloroethyl)-4,5-dihydro-1,3-oxazoles **2e** and **2d** behave differently. Compound **2d** reacts with nitrone **3a** to furnish 1,6-dioxa-2,9-diazaspiro[4.4]nonanes **17b** and **18b** after short reaction times, while **17b** converts over time into oxazetidine **19**. The reactions between α-lithiated 2-(chloromethyl)-4,5-dihydro-1,3-oxazole **2e** and nitrones **3** stereoselectively provides 2-[(*Z*)-alkenyl]-4,5-dihydro-1,3-oxazoles **26**. A detailed ^{1}H NMR examination of the reaction mixture at short reaction times allowed us to isolate and identify the precursors of 2-alkenyl-4,5-dihydro-1,3-oxazoles **26**. In any case, this work has allowed the development of a stereoselective method of preparation of 2-[(*Z*)- and (*E*)-alkenyl]-4,5-dihydro-1,3-oxazoles, which are potentially useful Michael acceptors and activated dienophiles. Moreover, the elucidation of the reaction paths should be useful in the future for selection of appropriate experimental conditions for the preparation of 1,6-dioxa-2,9-diazaspiro[4.4]nonanes, 2-(1,2-oxazetidin-4-yl)-4,5-dihydro-1,3-oxazoles, and isoxazolidin-5-ones.

Table 2. Synthesis of 2-[(*Z*)-alkenyl]-4,5-dihydro-1,3-oxazoles **26**



2e **3a-h** **26a-h**

Nitrone	R	Compound (yield%)[a][b]	Conversion (%)	(*Z*)/(*E*)[c]
3a	Ph	**26a** (46)	75	97:3
3b	*p*-MeC_6H_4	**26b** (67)	57	97:3
3c	*p*-ClC_6H_4	**26c** (66)	77	97:3
3d	*p*-$CH_3OC_6H_4$	**26d** (57)	50	97:3
3e	2,4,6-$(CH_3O)_3C_6H_2$	**26e**[d]	–	–
3f	3,4-(methylenedioxy)C_6H_3	**26f** (38)	86	94:6
3g	cyclohexyl	**26g** (55)	> 95	90:10
3h	$CH_3(CH_2)_6$	**26h** (49)	45	90:10
3i	*p*-$O_2NC_6H_4$	**26i**[d]	–	–

[a] Based on the converted nitrone. [b] Yields were not optimized. [c] Determined by ^{1}H NMR analysis. [d] No reaction.

Experimental Section

General Remarks: Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under nitrogen. Diisopropylamine and TMEDA were distilled from finely powdered calcium hydride. All the other chemicals were of commercial grade (Aldrich) and were used without further purification. "Petroleum ether" refers to the fraction boiling at 40−60 °C. Commercial solutions of *n*BuLi (in hexanes) and *s*BuLi (in cyclohexane) from Aldrich were titrated with *N*-pivaloyl-*o*-toluidine prior to use.[16] NMR: Bruker (300 or 500 MHz and 75.4 or 125 MHz, for ^{1}H and ^{13}C, respectively). For ^{1}H NMR, $CDCl_3$ as solvent, δ_H = 7.26 ppm; for ^{13}C NMR, $CDCl_3$ as solvent, δ_C = 77.0 ppm. FT-IR: Perkin−Elmer Spectrum One. GC-MS spectrometry analyses were performed with an HP 6890 gas chromatograph (HP-5MS capillary column, 30 m, 0.25 mm i.d.) equipped with a mass-selective detector operating at 70 eV (EI). Electron Spray Ionization (ESI) mass spectrometry was carried out with a LCQ-Finnigan Mat single quadrupole ion trap mass spectrometer, coupled with an Excalibur data system. Melting points were uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; viewing was accomplished by UV light (254 nm). Column chromatography was performed on silica gel (70−230 mesh), with petroleum ether (or hexane)/Et_2O (or EtOAc) mixture as eluent. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware by syringe/septum cap techniques. Spectroscopic data for compounds **8b** and **26b** have been reported in ref.[4]

Typical Procedure for the Synthesis of Compounds 6, 8a−h, 9, 10, 15, 17b, 18b, and 19: A solution of 4,5-dihydro-1,3-oxazole **1a** (or **1b**, **1c**, or **1d**, 0.66 mmol) in 1.3 mL of THF was added dropwise under N_2 to a precooled (−98 °C with a methanol/liquid nitrogen bath) solution of LDA (0.66 mmol) in dry THF (5 mL), and the resulting mixture was stirred at this temperature for 20 min. In the case of **15**, to a precooled (−78 °C) solution of **1c** (0.66 mmol) and TMEDA (0.92 mmol) in dry THF (5 mL), *s*BuLi (0.92 mmol) was added dropwise and the resulting mixture was stirred at this temperature for 1 h. After this time, a solution of nitrone **3** (0.60 mmol) in 1.3 mL of THF was added dropwise at −98 °C. When the reaction mixture was stirred for only 10 min, quenched with sat. aq. NH_4Cl, extracted with Et_2O (3 × 10 mL), and concentrated in vacuo, compounds **6**, **9**, **17b**, **18b**, and **19** could be obtained. When the reaction mixture was stirred overnight and then quenched with sat. aq. NH_4Cl, a similar workup provided (*E*)-alkenes **8a−h**. All these compounds could be purified by flash chromatography on silica gel (petroleum ether/EtOAc, 9−8:1−2).

2-{2-[*tert*-Butyl(hydroxy)amino]-2-phenylethyl}-4,4-dimethyl-4,5-dihydro-1,3-oxazole (6): Yield: 136 mg (78%), m.p. 114−115 °C (*n*-hexane). MS (ESI): *m*/*z* = 313 (6) $[M + Na]^+$, 290 (10) $[M]^+$, 289 (10), 233 (19) $[M^+ - t\text{Bu}]$, 202 (100) $[M^+ - t\text{BuNOH}]$. FT-IR (KBr): $\tilde{\nu}$ = 3251 (br., OH) cm^{-1}, 1652 (C=N), 1363, 701. $C_{17}H_{26}N_2O_2$ (290.40): calcd. C 70.31, H 9.02, N 9.65; found C 69.91, H 9.27, N 9.35. In $CDCl_3$ solution, it equilibrates to a mixture of the two diastereomeric 2-*tert*-butyl-8,8-dimethyl-3-phenyl-1,6-dioxa-2,9-diazaspiro[4.4]nonanes **7** [**7**/**6** = 7.1:1; *dr*(**7**) = 7:3]: ^{1}H NMR (500 MHz): δ = 0.91 (s, 9 H, *N*-*t*Bu-*H*, compd. **7** major), 0.97 (s, 9 H, *N*-*t*Bu-*H*, compd. **6**), 0.98 (s, 9 H, *N*-*t*Bu-*H*, compd. **7** minor), 1.17 and 1.33 (2 × s, 2 × 3 H, 2 × CH_3 dihydrooxazolyl, compd. **6**), 1.18 and 1.32 (2 × s, 2 × 3 H, 2 × CH_3 dihydrooxazolyl, compd. **7** minor), 1.19 and 1.23 (2 × s, 2 × 3 H, 2 × CH_3 dihydrooxazolyl, compd. **7** major), 2.42−2.54 [m, 1 H (4-H, compd. **7** major) + 2 H (4-H + 4-H′, compd. **7** minor)], 2.54 and 2.71 (2 × dd, *J* = 9.0, 13.0 Hz, 2 × 2 H, 4-H + 4-H′, compd. **6**), 3.09 (dd, *J* = 10.7, 13.5 Hz, 1 H, 4-H′, compd. **7** major), 3.65 and 3.71 (2 × d, AB system, *J* = 7.0 Hz, CH_2 dihydrooxazolyl, compd. **7** minor), 3.67 and 3.68 (2 × d, AB system, *J* = 7.3 Hz, CH_2 dihydrooxazolyl, compd. **6**), 3.87 and 3.88 (2 × d, AB system, *J* = 7.7 Hz, CH_2 dihydrooxazolyl, compd. **7** major), 4.17 (like t, *J* = 8.6 Hz, 1 H, 2-H, compd. **6**), 4.37 (dd, *J* = 6.0, 10.2 Hz, 1 H, 2-H, compd. **7** major), 4.46 (dd, *J* = 6.8, 12.0 Hz, 1 H, 2-H, compd. **7** minor), 7.18−7.38 (m, 3 × 3 H, Ar-*H*, compd. **6** + **7** major +**7** minor), 7.41−7.52 (m, 3 × 2 H, Ar-*H*, compd. **6** + **7** major + **7** minor) ppm. ^{13}C NMR (125 MHz) (selected data for compd. **6** + **7** major + **7** minor): δ = 25.9, 26.1, 26.6, 28.0, 28.1, 34.8, 50.2, 50.9, 57.3, 58.9, 62.0, 63.2, 63.5, 66.5, 72.4, 76.6, 76.9, 79.0, 117.5, 126.8, 126.9, 127.2, 127.8, 128.1, 129.0, 141.6, 142.7, 164.9 ppm.

(*E*)-4,4-Dimethyl-2-styryl-4,5-dihydro-1,3-oxazole (8a): Yield: 114 mg (95%), yellow oil, *dr* (*E*)/(*Z*) > 99:1. ^{1}H NMR (500 MHz): δ = 1.31 (s, 6 H), 4.00 (s, 2 H), 6.58 (d, *J* = 15.8 Hz, 1 H), 7.31 (d, *J* = 15.8 Hz, 1 H), 7.32−7.38 (m, 3 H), 7.41−7.45 (m, 2 H) ppm. ^{13}C NMR (75.4 MHz): δ = 28.5, 67.4, 78.9, 115.6, 127.5, 129.0, 129.5, 135.4, 139.8, 162.0 ppm. GC-MS (70 eV): *m*/*z* (%) = 201 (17) $[M^+]$, 186 (100), 130 (25), 115 (26). FT-IR (film): $\tilde{\nu}$ = 2967 cm^{-1}, 1655 (C=N), 1608 (C=C), 1355, 1004, 973, 758, 697.

(*E*)-2-[2-(4-Chlorophenyl)vinyl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (8c): Yield: 98 mg (70%), yellow oil, *dr* (*E*)/(*Z*) > 99:1. ^{1}H NMR (300 MHz): δ = 1.31 (s, 6 H), 4.00 (s, 2 H), 6.53 (d, *J* = 16.2 Hz, 1 H), 7.25 (d, *J* = 16.2 Hz, 1 H), 7.27−7.48 (m, 4 H) ppm. ^{13}C NMR (75.4 MHz): δ = 28.5, 67.5, 79.0, 116.3, 128.7, 129.3, 134.0, 135.4, 138.4, 161.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 236 (13) [M$^+$ + 2], 234 (30), 220 (100), 164 (24). FT-IR (film): ṽ = 2965 cm^{-1}, 1653 (C=N), 1604 (C=N), 1491, 1088.

(*E*)-2-[2-(4-Methoxyphenyl)vinyl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (8d): Yield: 105 mg (85%, based on 90% conversion), yellow oil, *dr* (*E*)/(*Z*) > 99:1. ^{1}H NMR (300 MHz): δ = 1.34 (s, 6 H), 3.83 (s, 3 H), 4.02 (s, 2 H), 6.47 (d, *J* = 16.2 Hz, 1 H), 6.89 (d, *J* = 8.7 Hz, 2 H), 7.29 (d, *J* = 16.2 Hz, 1 H), 7.42 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75.4 MHz): δ = 28.6, 55.6, 67.3, 79.0, 113.3, 114.5, 128.2, 129.1, 139.4, 160.8, 162.3 ppm. GC-MS (70 eV): *m*/*z* (%) = 230 (100) [M$^+$ − 1], 216 (33), 145 (20). FT-IR (film): ṽ = 2967 cm^{-1}, 1655 (C=N), 1603 (C=C), 1512, 1294.

(*E*)-4,4-Dimethyl-2-[2-(2,4,6-trimethoxyphenyl)vinyl]-4,5-dihydro-1,3-oxazole (8e): Yield: 116 mg (95%, based on 70% conversion), m.p. 140−142 °C (*n*-hexane), *dr* (*E*)/(*Z*) > 99:1. ^{1}H NMR (300 MHz): δ = 1.30 (s, 6 H), 3.80 (s, 3 H), 3.82 (s, 6 H), 3.98 (s, 2 H), 6.08 (s, 2 H), 6.99 (d, *J* = 16. 2 Hz, 1 H), 7.64 (d, *J* = 16.2 Hz, 1 H) ppm. ^{13}C NMR (75.4 MHz): δ = 28.4, 55.3, 55.6, 66.8, 78.5, 90.3, 106.3, 115.6, 130.2, 160.5, 161.8, 163.5 ppm. GC-MS (70 eV): *m*/*z* (%) = 291 (3) [M$^+$], 260 (100), 205 (15). FT-IR (KBr): ṽ = 2970 cm^{-1}, 1639 (C=N), 1606 (C=C), 1573, 1197, 1118, 800. $C_{16}H_{21}NO_4$ (291.34): C 65.96, H 7.27, N 4.81; found C 65.78, H 7.28, N 4.79.

2-[(*E*)-2-(1,3-Benzodioxol-5-yl)vinyl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (8f): Yield: 102 mg (70%), yellow oil, *dr* (*E*)/(*Z*) > 99:1. ^{1}H NMR (300 MHz): δ = 1.34 (s, 6 H), 4.02 (s, 2 H), 6.00 (s, 2 H), 6.43 (d, *J* = 16.2 Hz, 1 H), 6.79−6.85 (m, 2 H), 6.88−6.95 (m, 2 H), 6.99 (s, 1 H), 7.25 (d, *J* = 16.2 Hz, 1 H) ppm. ^{13}C NMR (75.4 MHz): δ = 26.4, 65.2, 76.9, 99.8, 104.1, 106.6, 111.6, 121.3, 127.8, 137.3, 146.3, 146.8, 159.9 ppm. GC-MS (70 eV): *m*/*z* (%) = 244 (100) [M$^+$], 230 (40), 159 (23). FT-IR (film): ṽ = 2968, 1658 (C=N), 1608 (C=C), 1489, 1253, 1039, 808 cm^{-1}.

(*E*)-2-(2-Cyclohexylvinyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (8g): Yield: 74 mg (60%), colorless oil, *dr* (*E*)/(*Z*) > 99:1. ^{1}H NMR (300 MHz): δ = 1.02−1.25 (m, 10 H), 1.61−1.72 (m, 6 H), 2.05−2.07 (m, 1 H), 3.91 (s, 2 H), 5.85 (dd, *J* = 1.3, 15.9 Hz, 1 H), 6.47 (dd, *J* = 6.8, 15.9 Hz, 1 H) ppm. ^{13}C NMR (75.4 MHz): δ = 25.4, 25.9, 28.3, 31.8, 40.6, 66.8, 78.6, 115.5, 148.8, 161.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 207 (53) [M$^+$], 192 (100), 110 (90). FT-IR (film): ṽ = 2926 cm^{-1}, 1672 (C=N), 1610 (C=C), 1449, 976.

(*E*)-4,4-Dimethyl-2-(non-1-enyl)-4,5-dihydro-1,3-oxazole (8h): Yield: 70 mg (52%), colorless oil, *dr* (*E*)/(*Z*) > 99:1. ^{1}H NMR (300 MHz): δ = 0.84−1.00 (m, 6 H), 1.05−1.72 (m, 13 H), 2.12−2.25 (m, 2 H), 3.92 (s, 2 H), 5.90 (d, *J* = 15.9 Hz, 1 H), 6.54 (dt, *J* = 6.8, 15.9 Hz, 1 H) ppm. ^{13}C NMR (75.4 MHz): δ = 14.2, 22.8, 28.5, 29.3, 31.9, 32.7, 67.1, 79.3, 118.0, 144.1, 161.7 ppm. GC-MS (70 eV): *m*/*z* (%) = 223 (7) [M$^+$], 208 (100), 110 (33). FT-IR (film): ṽ = 2927 cm^{-1}, 1674 (C=N), 1612 (C=C), 1002, 974.

***trans*-2-*tert*-Butyl-4,8,8-trimethyl-3-phenyl-1,6-dioxa-2,9-diazaspiro[4.4]nonane (9):** Yield: 127 mg (70% yield, *dr* = 87:9/4 by ^{1}H NMR), m.p. 75−77 °C (*n*-hexane). ^{1}H NMR (300 MHz) (selected data for the *trans* major isomer): δ = 0.86 (d, *J* = 7.0 Hz, 3 H), 0.97 (s, 9 H), 1.17 (s, 3 H), 1.34 (s, 3 H), 2.04−2.26 (br. s, exchanges with D$_2$O, 1 H), 2.28−2.40 (m, 1 H), 3.58 and 3.73 (2 × d, AB system, *J* = 7.3 Hz, 2 H), 3.90 (d, *J* = 11.3 Hz, 1 H), 7.16−7.20 (m, 1 H), 7.22−7.28 (m, 2 H), 7.33−7.45 (m, 2 H) ppm. ^{13}C NMR (125 MHz) (selected data for the *trans* major isomer): δ = 9.0, 26.1, 26.8, 28.3, 52.3, 55.9, 59.2, 69.1, 76.7, 119.2 (*C* spiro), 126.8, 127.0, 128.0, 142.5 ppm. GC-MS (70 eV): *m*/*z* (%) = 304 (1) [M$^+$], 214 (100), 200 (28), 127 (23), 115 (28), 91 (15), 57 (14), 41 (12). FT-IR (film): ṽ = 3353 (N−H) cm^{-1}, 2972, 1464, 1381, 1362, 1049, 994, 844, 691, 600. $C_{18}H_{28}N_2O_2$ (304.43): calcd. C 71.01, H 9.27, N 9.20; found C 69.93, H 9.48, N 8.91.

***N*-*tert*-Butyl-*N*-[(2-*tert*-butyl-4,8,8-trimethyl-3-phenyl-1,6-dioxa-2,9-diazaspiro[4.4]non-4-yl)phenylmethyl]hydroxylamine (10):** Yield: 14 mg (5% yield, *dr* = 95:5 by ^{1}H NMR), m.p. 122−124 °C (*n*-hexane). ^{1}H NMR (300 MHz) (selected data for the major isomer): δ = 0.71 (s, 3 H), 0.99 (s, 9 H), 1.00 (s, 9 H), 1.19 (s, 3 H), 1.23 (s, 3 H), 1.8−1.9 (br. s, exchanges with D$_2$O, 2 H), 3.74 (s, 1 H), 3.75 (d, *J* = 10.8 Hz, 1 H), 4.38 (s, 1 H), 5.04 (d, *J* = 7.8 Hz, 1 Ar-*H*), 6.74−7.50 (8 m, 8 Ar-*H*), 7.92 (d, *J* = 7.7 Hz, 1 Ar-*H*) ppm. ^{13}C NMR (125 MHz) (selected data for the major isomer): δ = 21.8, 25.8, 26.7, 26.9, 28.8, 53.9, 58.6, 59.9, 66.1, 67.8, 69.5, 75.8, 117.3, 126.5, 127.0, 127.4, 127.8, 128.0, 128.3, 129.8, 130.5, 138.6, 140.0 ppm. MS (ESI): *m*/*z* = 504 (20) [M + Na]$^+$ 482 (100) [M + H]$^+$. FT-IR (KBr): ṽ = 3483 cm^{-1}, 3401, 2973, 1362, 1215, 1056, 709. $C_{29}H_{43}N_3O_3$ (481.67): calcd. C 72.31, H 9.00, N 8.72; found C 71.93, H 8.78, N 8.53.

2-*tert*-Butyl-4,4,8,8-tetramethyl-3-phenyl-1,6-dioxa-2,9-diazaspiro[4.4]nonane (15): Yield: 131 mg (69% yield, *dr* = 95:5 by ^{1}H NMR), m.p. 67−69 °C (*n*-hexane). ^{1}H NMR (300 MHz) (selected data for the major isomer): δ = 0.80 (s, 3 H), 0.88 (s, 3 H), 0.99 (s, 9 H), 1.18 (s, 3 H), 1.35 (s, 3 H), 1.8−1.9 (br. s, exchanges with D$_2$O, 1 H), 3.64 and 3.78 (2 × d, AB system, *J* = 7.5 Hz, 2 H), 4.24 (s, 1 H), 7.04−7.07 (m, 1 H), 7.19−7.32 (m, 3 H), 7.73−7.75 (m, 1 H) ppm. ^{13}C NMR (125 MHz) (selected data for the major isomer): δ = 19.2, 20.0, 26.9, 27.4, 28.9, 48.9, 55.9, 59.5, 70.9, 77.3, 121.9 (*C* spiro), 126.9, 127.3, 127.5, 129.2, 140.5 ppm. GC-MS (70 eV): *m*/*z* (%) = 318 (1) [M$^+$], 232 (39), 192 (4), 175 (12), 148 (15), 105 (100), 77 (25), 58 (8). FT-IR (KBr): ṽ = 3378 (N−H) cm^{-1}, 2973, 1454, 1362, 1258, 1217, 1084, 1032, 971, 707. $C_{19}H_{30}N_2O_2$ (318.45): calcd. C 71.66, H 9.49, N 8.80; found C 71.65, H 9.60, N 8.61.

(3*R,4*S**,5*R**)-2-*tert*-Butyl-4-chloro-4,8,8-trimethyl-3-phenyl-1,6-dioxa-2,9-diazaspiro[4.4]nonane (17b):** Overall yield: 116 mg (57%), **17b/18b** = 5:1, m.p. 81−82 °C (*n*-hexane). ^{1}H NMR (500 MHz): δ = 0.99 (s, 9 H), 1.25 (s, 3 H), 1.33 (s, 3 H), 1.36 (s, 3 H), 2.0−2.2 (br. s, 1 H, exchanges with D$_2$O), 3.78 (d, *J* = 7.6 Hz, 1 H), 3.83 (d, *J* = 7.6 Hz, 1 H), 4.62 (s, 1 H), 7.23−7.31 (m, 4 H), 7.68−7.70 (m, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 22.7, 26.7, 27.1, 27.8, 60.2, 70.7, 73.5, 77.9, 107.5, 127.3, 127.9, 128.8, 129.0, 137.6 ppm. GC-MS (70 eV): *m*/*z* (%) = 340 (1) [M$^+$ + 2], 338 (2) [M$^+$], 216 (42), 178 (29), 161 (100), 122 (60), 57 (14), 41 (7). FT-IR (KBr): ṽ = 3374 (sharp, N−H) cm^{-1}, 1455, 1255, 1077, 704. $C_{18}H_{27}ClN_2O_2$ (338.18): calcd. C 63.80, H 8.03, N 8.27, found C 64.12, H 8.31, N 8.56.

(3*R,4*R**,5*R**)-2-*tert*-Butyl-4-chloro-4,8,8-trimethyl-3-phenyl-1,6-dioxa-2,9-diazaspiro[4.4]nonane (18b):** M.p. 101−102 °C (*n*-hexane). ^{1}H NMR (500 MHz): δ = 1.00 (s, 9 H), 1.23 (s, 3 H), 1.38 (s, 3 H), 1.43 (s, 3 H), 2.42 (br. s, 1 H, exchanges with D$_2$O), 3.71 (d, *J* = 7.2 Hz, 1 H), 3.89 (d, *J* = 7.2 Hz, 1 H), 4.41 (s, 2 H), 7.06−7.07 (m, 1 H), 7.23−7.29 (m, 2 H), 7.31−7.34 (m, 1 H), 7.90−7.92 (m, 1 H) ppm. ^{13}C NMR (125 MHz): δ = 21.2, 26.9, 27.6, 28.3, 56.3, 59.8, 70.8, 78.6, 79.2, 120.4, 127.4, 127.9, 130.7, 138.0 ppm. GC-MS (70 eV): *m*/*z* (%) = 340 (1) [M$^+$ + 2], 338 (3) [M$^+$], 216 (44), 178 (30), 161 (100), 122 (54). FT-IR (KBr): ṽ = 3393 (sharp, N−H) cm^{-1}, 1455, 1379, 1057, 971. $C_{18}H_{27}ClN_2O_2$ (338.18): calcd. C 63.80, H 8.03, N 8.27; found C 64.19, H 8.41, N 8.28.

(3*R,4*S**)-2-(2-*tert*-Butyl-4-methyl-3-phenyl-1,2-oxazetidin-4-yl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (19):** Yield: 70 mg (39%), m.p.

79−80 °C (*n*-hexane). ^{1}H NMR (500 MHz): δ = 1.09 (s, 9 H), 1.28 (s, 3 H), 1.32 (s, 3 H), 1.34 (s, 3 H), 4.03 (s, 2 H), 5.47 (s, 1 H), 7.26−7.55 (2 m, 5 H) ppm. ^{13}C NMR (75.4 MHz, DEPT): δ = 21.2 (*C*H$_3$), 23.7 (*C*H$_3$), 28.2 (*C*H$_3$), 59.2, 65.5 (*C*H), 67.4, 78.1, 79.7 (*C*H$_2$), 127.5 (Ar*C*H), 128.1 (Ar*C*H), 137.4 (*C ipso*), 165.4 (*C*=N). Two complementary fragments corresponding to 4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl methyl ketone (M. W. 141) and to *N*-*tert*-butylbenzylideneamine (M. W. 161) were observed in the GC-MS of **19** at 70 eV, with the following fragmentations (respectively): *m*/*z* (%) = 141 (6) [M$^+$], 126 (2), 84 (68), 69 (89), 56 (100), 41 (76); *m*/*z* (%) = 161 (10) [M$^+$], 160 (5), 146 (100), 106 (24), 104 (25), 89 (10), 77 (11), 57 (20), 41 (10). FT-IR (KBr): ṽ = 1663 (C=N), cm^{-1}, 1451, 1365, 1244, 1088. $C_{18}H_{26}N_2O_2$ (302.20): C 71.49, H 8.67, N 9.26; found C 71.87, H 8.98, N 9.06.

Typical Procedure for the Synthesis of Compounds 21-H, 23-H, 24-H, 25a, 25c, 26a−d, 26f−h, 27a, and 27c: A solution of 2-(chloromethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**1e**) (97 mg, 0.66 mmol) and nitrone **3** (0.60 mmol) in 3 mL of THF was added dropwise under N_2 to a precooled (−98 °C with a methanol/liquid nitrogen bath) solution of LDA (0.66 mmol) in dry THF (5 mL), and the resulting mixture was stirred overnight, quenched with sat. aq. NH_4Cl, extracted with Et_2O (3 × 10 mL), and concentrated in vacuo. Compounds **25a**, **25c**, **26a−d, 26f−h**, **27a**, and **27c** could be isolated by flash chromatography on silica gel (petroleum ether/Et_2O, 3:2). On the other hand, compounds **21-H**, **23-H**, and **24-H** could be isolated by quenching the reaction mixture after 1 min and usual workup as described above.

***trans*-2-*tert*-Butyl-4-chloro-8,8-dimethyl-3-phenyl-1,6-dioxa-2,9-diazaspiro[4.4]nonane (21-H):** Yield: 14 mg (7% yield, *dr* = 86:14 by ^{1}H NMR), m.p. 89−91 °C (*n*-hexane). ^{1}H NMR (500 MHz) (selected data): δ = 0.99 (s, 2 × 9 H, major + minor), 1.21 (s, 3 H, minor), 1.24 (s, 3 H, major), 1.33 (s, 3 H, minor), 1.35 (s, 3 H, major), 2.2−2.5 (br. s, exchanges with D_2O, 2 × 1 H), 3.71 and 3.82 (2 × d, AB system, *J* = 7.7 Hz, 2 H, minor), 3.74 and 3.82 (2 × d, AB system, *J* = 7.3 Hz, 2 H, major), 4.09 (d, *J* = 6.4 Hz, 1 H, minor),4.10 (d, *J* = 10.7 Hz, 1 H, major), 4.29 (d, *J* = 10.7 Hz, 1 H, major),4.36 (d, *J* = 6.4 Hz, 1 H, minor), 7.24−7.40 (m, 2 × 3 H, major + minor), 7.45−7.58 (m, 2 × 2 H, major + minor) ppm. ^{13}C NMR (125 MHz) (selected data): δ = 26.1 (minor), 26.2 (major), 26.6 (minor), 27.0 (major), 27.2 (minor), 27.6 (major), 56.9, 57.7, 58.8, 60.3, 67.3, 67.5, 68.8, 73.0, 73.4, 77.9 (minor), 78.0 (major), 116.7 (*C* spiro minor),116.8 (*C* spiro major), 127.5, 127.8, 128.0, 128.4, 128.5, 139.6, 139.7 ppm. MS (ESI): *m*/*z* = 327 (33) [M + 2 + H]$^+$, 325 (100) [M + H]$^+$, 236 (5), 178 (25), 122 (7). FT-IR (KBr): ṽ = 3354 (N−H) cm^{-1}, 2973, 2878, 1466, 1383, 1359, 1210, 1040, 972, 766. $C_{17}H_{25}ClN_2O_2$ (324.85): calcd. C 62.85, H 7.75, N 8.62; found C 62.65, H 7.52, N 8.41.

***threo*- and *erythro*-*N*-*tert*-Butyl-*N*-[2-chloro-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-1-phenylethyl]hydroxylamine (23-H + 24-H):** Yield: 86 mg (44%), m.p. 122−124 °C (*n*-hexane). MS (ESI): *m*/*z* = 327 (33) [M + 2 + H]$^+$, 325 (100) [M + H]$^+$, 267 (1), 236 (14), 178 (29), 122 (8). FT-IR (KBr): ṽ = 3290 cm^{-1}, 2970, 1669 (C=N), 699, 657. $C_{17}H_{25}ClN_2O_2$ (324.85): calcd. C 62.86, H 7.76, N 8.62; found C 62.47, H 8.60, N 7.53. In $CDCl_3$ solution, they equilibrate to a mixture of the corresponding diastereomeric *trans*- and *cis*-2-*tert*-butyl-4-chloro-8,8-dimethyl-3-phenyl-1,6-dioxa-2,9-diazaspiro[4.4]nonanes (**21-H** + **22-H**) [(**23-H** + **24-H**)/(**21-H** + **22-H**) = 9:1; **23-H/24-H** = 85:15; **22-H/21-H** = 4:1]. ^{1}H NMR (500 MHz) (selected data): δ = 1.02 (s, 9 H, *N*-*t*Bu-*H*, *threo*), 1.04 (s, 9 H, *N*-*t*Bu-*H*, *erythro*), 1.22 (s, 3 H, C*H*$_3$, *threo*), 1.35 (s, 3 H, C*H*$_3$, *threo*), 2.20−2.70 (br.s, exchanges with D_2O, 2 × 1 H, N*H*), 3.59 (d, *J* = 10.7 Hz, 1 H, C*H*O dihydrooxazolyl, *erythro*), 3.75 and 3.88 (2 × d, AB system, *J* = 7.7 Hz, 2 H, C*H*$_2$O dihydrooxazolyl, *threo*), 3.77 and 3.94 (2 × d, AB system, *J* = 7.8 Hz, 2 H, C*H*$_2$O dihydrooxazolyl, *cis*), 4.22 (d, *J* = 4.3 Hz, 1 H, C*H*Cl, *threo*), 4.32 (d, *J* = 10.3 Hz, 1 H, C*H*Cl, *erythro*), 4.42 and 4.46 (2 × d, AB system, *J* = 10.4 Hz, 2 H, isoxazolidinyl, *cis*), 4.60−4.80 (br.s, exchanges with D_2O, 2 × 1 H, O*H*), 4.87 (d, *J* = 4.3 Hz, 1 H, C*H*Ph, *threo*), 5.12 (d, *J* = 10.3 Hz, 1 H, C*H*Ph, *erythro*), 7.18−7.36 (m, 4 × 3 H, Ar-*H*, *threo* + *erythro* + *cis* + *trans*), 7.42−7.52 (m, 4 × 2 H, Ar-*H*, *threo* + *erythro* + *cis* + *trans*).

***trans*-2-(2-*tert*-Butyl-3-phenyl-1,2-oxazetidin-4-yl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (25a):** Yield: 38 mg (22%), yellow oil. ^{1}H NMR (500 MHz): δ = 1.07 (s, 9 H), 1.28 (s, 2 × 3 H), 3.99 and 4.01 (2 × d, AB system, *J* = 7.6 Hz, 2 H, C*H*$_2$O dihydrooxazolyl hydrogen atoms), 5.16 and 5.22 (2 × d, AB system, *J* = 8.1 Hz, 2 H, oxazetidine vicinal hydrogen atoms), 7.24−7.40 (2 m, 3 H), 7.50−7.65 (m, 2 H) ppm. ^{13}C NMR (125 MHz): δ = 23.2, 27.8, 27.9, 59.5, 62.8, 67.0, 75.5, 79.0, 127.8, 136.8, 162.2 ppm. MS (ESI): *m*/*z* = 289 (100) [M + H]$^+$, 202 (10). FT-IR (film): ṽ = 2970 cm^{-1}, 1681 (C=N), 1455, 1364, 1070, 699.

***trans*-2-[2-*tert*-Butyl-3-(4-chlorophenyl)-1,2-oxazetidin-4-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (25c):** Yield: 23 mg (12%, based on 77% conversion), yellow oil. ^{1}H NMR (500 MHz): δ = 1.07 (s, 9 H), 1.29 (s, 3 H), 1.30 (s, 3 H), 4.01 and 4.03 (2 × d, AB system, *J* = 8.0 Hz, 2 H), 5.11 and 5.19 (2 × d, AB system, *J* = 8.1 Hz, 2 H), 7.30−7.36 (m, 2 H), 7.52−7.56 (m, 2 H) ppm. ^{13}C NMR (125 MHz): δ = 23.4, 28.0, 28.2, 59.6, 64.3, 67.5, 76.0, 79.6, 128.6, 128.7, 134.0, 137.4, 161.5. Two complementary fragments corresponding to 4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-carbaldehyde (M. W. 127) and to *N*-*tert*-butyl(*p*-chlorobenzylidene)amine (M. W. 195) were observed in the GC-MS of **25c** at 70 eV, with the following fragmentations (respectively): *m*/*z* (%) = 127 (47) [M$^+$], 112 (19), 97 (100), 69 (32), 57 (37), 42 (95): *m*/*z* (%) = 195 (12) [M$^+$], 182 (38), 180 (100), 138 (20), 82 (24), 57 (90). FT-IR (film): ṽ = 2970 cm^{-1}, 1664 (C=N), 1491, 1364, 1089, 1014, 990.

(*Z*)-4,4-Dimethyl-2-styryl-4,5-dihydro-1,3-oxazole (26a): Yield: 42 mg (46%, based on 75% conversion), yellow oil, *dr* (*Z*)/(*E*) = 97:3. ^{1}H NMR (300 MHz) (selected data): δ = 1.27 (s, 6 H), 3.88 (s, 2 H), 6.01 (d, *J* = 12.6 Hz, 1 H), 6.83 (d, *J* = 12.6 Hz, 1 H), 7.32−7.45 (m, 5 H) ppm. ^{13}C NMR (75.4 MHz) (selected data): δ = 28.3, 67.1, 79.0, 116.8, 128.0, 128.5, 129.7, 135.8, 139.4, 161.3 ppm. GC-MS (70 eV): *m*/*z* (%) = 200 (100) [M$^+$ − 1], 186 (24), 130 (20), 115 (22). FT-IR (film): ṽ = 2967 cm^{-1}, 1655 (C=N), 1607 (C=C), 1355, 1001, 974, 759, 696.

(*Z*)-2-[2-(4-Chlorophenyl)vinyl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (26c): Yield: 69 mg (66%, based on 77% conversion), yellow oil, *dr* (*Z*)/(*E*) = 97:3. ^{1}H NMR (300 MHz) (selected data): δ = 1.30 (s, 6 H), 3.91 (s, 2 H), 6.04 (d, *J* = 12.6 Hz, 1 H), 6.80 (d, *J* = 12.6 Hz, 1 H), 7.28 (d, *J* = 7.0 Hz, 2 H), 7.43 (d, *J* = 7.0 Hz, 2 H) ppm. ^{13}C NMR (75.4 MHz) (selected data): δ = 28.3, 67.3, 79.0, 117.5, 128.2, 131.1, 134.3, 134.4, 138.1, 161.0 ppm. GC-MS (70 eV): *m*/*z* (%) = 236 (38) [M$^+$ + 2], 234 (100), 220 (22), 164 (17). FT-IR (film): ṽ = 2967 cm^{-1}, 1657 (C=N), 1588 (C=C), 1491, 1091.

(*Z*)-2-[2-(4-Methoxyphenyl)vinyl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (26d): Yield: 40 mg (57%, based on 50% conversion), yellow oil, *dr* (*Z*)/(*E*) = 97:3. ^{1}H NMR (300 MHz) (selected data): δ = 1.31 (s, 6 H), 3.80 (s, 3 H), 3.93 (s, 2 H), 5.90 (d, *J* = 12.2 Hz, 1 H), 6.76 (d, *J* = 12.2 Hz, 1 H), 6.83 (d, *J* = 8.4 Hz, 2 H), 7.50 (d, *J* = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75.4 MHz) (selected data): δ = 28.4, 55.4, 67.1, 78.9, 113.4, 114.6, 128.4, 131.6, 139.0, 159.9, 161.5 ppm. GC-MS (70 eV): *m*/*z* (%) = 230 (100) [M$^+$ − 1], 216 (21), 145 (18). FT-IR (film): ṽ = 2967 cm^{-1}, 1655 (C=N), 1604 (C=C), 1511, 1252.

2-[(*Z*)-2-(1,3-Benzodioxol-5-yl)vinyl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (26f): Yield: 48 mg (38%, based on 86% conversion), yellow oil, *dr* (*Z*)/(*E*) = 94:6. ^{1}H NMR (300 MHz) (selected data): δ = 1.30 (s, 6 H), 3.93 (s, 2 H), 5.89 (d, *J* = 12.8 Hz, 1 H), 5.94 (s, 2 H), 6.71 (d, *J* = 12.8 Hz, 1 H), 6.74 (d, *J* = 8.0 Hz, 1 H), 6.93 (dd, *J* = 8.0, 1.3 Hz, 1 H), 7.25 (d, *J* = 1.3 Hz, 1 H) ppm. ^{13}C NMR (75.4 MHz) (selected data): δ = 28.1, 64.0, 78.7, 101.1, 107.7, 109.6, 111.4, 111.6, 114.7, 123.1, 124.7, 138.7, 170.8 ppm. GC-MS (70 eV): *m*/*z* (%) = 244 (100) [M$^+$], 230 (20), 159 (26). FT-IR (film): $\tilde{\nu}$ = 2967cm^{-1}, 1654 (C=N), 1606 (C=C), 1490, 1446, 1241, 1039.

(*Z*)-2-(2-Cyclohexylvinyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (26g): Yield: 68 mg (55%), colorless oil, *dr* (*Z*)/(*E*) = 90:10. ^{1}H NMR (300 MHz) (selected data): δ = 0.98−1.44 (m, 10 H), 1.58−1.84 (m, 6 H), 2.96−3.06 (m, 1 H), 3.97 (s, 2 H), 5.71 (d, *J* = 12.0 Hz, 1 H), 5.78 (dd, *J* = 9.4, 12.0 Hz, 1 H) ppm. ^{13}C NMR (75.4 MHz) (selected data): δ = 25.7, 26.1, 28.5, 32.9, 37.9, 66.3, 79.1, 114.7, 149.7, 162.2 ppm. GC-MS (70 eV): *m*/*z* (%) = 207 (40) [M$^+$], 110 (38), 55 (39), 41 (100). FT-IR (film): $\tilde{\nu}$ = 2926 cm^{-1}, 1664 (C=N), 1638 (C=C), 1448, 999.

(*Z*)-4,4-Dimethyl-2-(non-1-enyl)-4,5-dihydro-1,3-oxazole (26h): Yield: 29 mg (49%, based on 45% conversion), colorless oil, *dr* (*Z*)/(*E*) = 90:10. ^{1}H NMR (300 MHz) (selected data): δ = 0.84−0.88 (m, 6 H), 1.14−1.61 (m, 13 H), 2.36−2.62 (m, 2 H), 3.94 (s, 2 H), 5.81 (d, *J* = 11.8 Hz, 1 H), 6.80 (dt, *J* = 11.8, 7.5 Hz, 1 H) ppm. ^{13}C NMR (75.4 MHz) (selected data): δ = 14.3, 22.8, 28.5, 29.3, 29.4, 32.0, 32.7, 66.6, 78.8, 116.5, 144.7, 162.2 ppm. GC-MS (70 eV): *m*/*z* (%) = 223 (8) [M$^+$], 208 (21), 152 (100). FT-IR (film): $\tilde{\nu}$ = 2926 cm^{-1}, 1666 (C=N), 1643 (C=C), 1000.

***cis*-2-(2-*tert*-Butyl-3-phenyl-1,2-oxazetidin-4-yl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (27a):** Yield: 12 mg (7%), yellow oil. ^{1}H NMR (300 MHz): δ = 0.82 (s, 3 H), 1.04 (s, 3 H), 1.14 (s, 9 H), 3.53 and 3.56 (2 × d, AB system, *J* = 8.1 Hz, 2 H), 5.27 and 5.56 (2 × d, AB system, *J* = 10.0 Hz, 2 H, oxazetidine vicinal hydrogens), 7.27−7.36 (m, 3 H), 7.56−7.58 (m, 2 H) ppm. ^{13}C NMR (125 MHz): δ = 22.5, 27.0, 27.2, 58.6, 64.0, 66.4, 75.1, 78.5, 126.2, 127.1, 127.5, 137.8, 160.6 ppm. MS (ESI): *m*/*z* = 289 (100) [M + H]$^+$, 202 (2). FT-IR (film): $\tilde{\nu}$ = 2970 cm^{-1}, 1667 (C=N), 1364, 990, 733, 700.

***cis*-2-[2-*tert*-Butyl-3-(4-chlorophenyl)-1,2-oxazetidin-4-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (27c):** Yield: 33 mg (17%, based on 77% conversion), yellow waxy solid. ^{1}H NMR (300 MHz): δ = 0.82 (s, 3 H), 1.00 (s, 3 H), 1.07 (s, 9 H), 3.50 and 3.55 (2 × d, AB system, *J* = 7.9 Hz, 2 H), 5.17 (d, *J* = 10.0 Hz, 1 H), 5.48 (d, *J* = 10.0 Hz, 1 H), 7.10−7.13 (m, 2 H), 7.40−7.50 (m, 2 H) ppm. ^{13}C NMR (125 MHz): δ = 23.1, 27.8, 27.9, 59.5, 62.0, 67.1, 75.3, 79.1, 127.9, 129.3, 133.6, 161.9. Two complementary fragments corresponding to 4,4-dimethyl-4,5-dihydro-1,3-oxazole-2-carbaldehyde (M. W. 127) and to *N*-*tert*-butyl(*p*-chlorobenzylidene)amine (M. W. 195) were observed in the GC-MS of **27c** at 70 eV, with the following fragmentations (respectively): *m*/*z* (%) = 127 (47) [M$^+$], 112 (19), 97 (100), 69 (32), 57 (37), 42 (95): *m*/*z* (%) = 195 (12) [M$^+$], 182 (38), 180 (100), 138 (20), 82 (24), 57 (90). FT-IR (film): $\tilde{\nu}$ = 2965 cm^{-1}, 1661 (C=N), 1490, 1259, 1089, 1016, 803.

Hydrolysis of Spirocyclic Compounds 9 and 15: An aq. solution of $(COOH)_2$ (2% w/w, 1.32 mmol) was added to a solution of the spirocyclic compound **9** or **15** in THF (0.66 mmol in 3 mL), and the resulting mixture was stirred at room temp. for 24 h. After this time, the mixture was poured into brine, extracted with EtOAc (3 × 10 mL), and concentrated in vacuo. Flash chromatography on silica gel (petroleum ether/EtOAc, 4:1) afforded the following compounds, respectively.

(*Z*)-4,4-Dimethyl-2-(1-methyl-2-phenylvinyl)-4,5-dihydro-1,3-oxazole (14): Yield: 13 mg [quantitative yield of (*Z*) and (*E*) isomers, (*E*)/(*Z*) = 9:1], oil. ^{1}H NMR (300 MHz): δ = 1.29 (s, 2 × 3 H, 2 × CH_3 oxazoline), 2.16 (d, *J* = 0.8 Hz, 3 H, CH_3 C=), 3.85 (s, 2 H, CH_2 oxazoline), 6.71 (m, 1 H, vinylic H), 7.18−7.42 (2 m, 5 H, Ar-*H*) ppm. ^{13}C NMR (125 MHz): δ = 22.9, 28.0, 67.1, 78.7, 127.3, 127.7, 128.4, 134.3, 136.7, 163.2 ppm. GC-MS (70 eV): *m*/*z* (%) = 214 (100) [M$^+$ − 1], 115 (23), 55 (40). FT-IR (KBr): $\tilde{\nu}$ = 2925 cm^{-1}, 1644 (C=N), 1614, 1094, 696.

(*E*)-4,4-Dimethyl-2-(1-methyl-2-phenylvinyl)-4,5-dihydro-1,3-oxazole (14): Yield: 114 mg [quantitative yield of (*Z*) and (*E*) isomers, (*E*)/(*Z*) = 9:1], oil. ^{1}H NMR (300 MHz): δ = 1.34 (s, 2 × 3 H, 2 × CH_3 dihydrooxazolyl), 2.18 (d, *J* = 1.4 Hz, 3 H, CH_3 C=), 4.02 (s, 2 H, CH_2 dihydrooxazolyl), 7.15−7.45 (2 m, 6 H, Ar-*H* + 1 vinylic *H*) ppm. ^{13}C NMR (125 MHz): δ = 15.1, 28.3, 67.4, 78.8, 127.6, 128.2, 129.4, 134.8, 136.3, 164.1 ppm. GC-MS (70 eV): *m*/*z* (%) = 214 (100) [M$^+$ − 1], 200 (30), 115 (30). FT-IR (KBr): $\tilde{\nu}$ = 2966 cm^{-1}, 1643 (C=N), 1614, 1090, 759, 707, 693.

2-*tert*-Butyl-4,4-dimethyl-3-phenylisoxazolidin-5-one (16): Yield: 77 mg (73% based on 65% conversion), m.p. 100−102 °C (*n*-hexane). ^{1}H NMR (500 MHz): δ = 0.92 (s, 3 H), 1.03 (s, 9 H), 1.18 (s, 3 H), 4.20 (s, 1 H), 7.01−7.68 (3 m, 5 H) ppm. ^{13}C NMR (125 MHz): δ = 21.2, 22.0, 25.9, 46.7, 60.9, 72.9, 127.1, 127.9, 128.0, 128.2, 128.9, 137.0, 178.4 ppm. GC-MS (70 eV): *m*/*z* (%) = 247 (8) [M$^+$], 232 (11), 146 (22), 104 (70), 57 (100). FT-IR (KBr): $\tilde{\nu}$ = 2977 cm^{-1}, 1770 (C=O), 1456, 1142, 705. $C_{15}H_{21}NO_2$ (247.16): calcd. C 72.84, H 8.56, N 5.66; found C 72.95, H 8.74, N 5.66.

X-ray Crystallographic Study: Crystallographic data and the most salient experimental parameters relating to the X-ray measurements and the crystal structure analysis for compounds **17b** and **18b** are reported in the Supporting Information. All diagrams and calculations were produced with maXus (Nonius, Delft & MacScience, Japan),[17] SIR92[18] and ORTEP.[19] CCDC-163503 and -163502 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[6] About a 20% yield of (*E*)-4,4-dimethyl-2-styryl-4,5-dihydro-1,3-oxazole (**8a**) was also formed. We presume it forms from **4** by elimination of *N*-*tert*-butylhydroxylamine. The (*Z*) and (*E*) configurations of the styrene derivatives obtained in the reactions of **2a** and **2d** were assigned on the basis of the coupling constants of the vinylic hydrogen atoms ($^3J_{H,H(E)}$ = 15.8 Hz; $^3J_{H,H(Z)}$ = 12.6 Hz).

[7] The (*E*) isomer should be the one with the more deshielded vinylic proton (see Exp. Sect.) with respect to the (*Z*) one, as reported (ref.[3d]) for other similar β-dihydrooxazolylstyrenes.

[8] 2-Isopropyl-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**1c**) was prepared by lithiation (LDA 2.5 equiv., THF, −98 °C, 3 h) of the commercially available 2-ethyl-4,4-dimethyl-4,5-dihydro-1,3-oxazole (quantitative yield); spectroscopic data have been reported in: H. Feuer, H. S. Bevinakatti, Xuan-Gan Luo, *J. Heterocycl. Chem.* **1986**, *23*, 825−832.

[9] 2-(1-Chloroethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**1d**) was prepared by chlorination of 2-ethyl-4,4-dimethyl-4,5-dihydro-1,3-oxazole (**1b**) with *tert*-butyl hypochlorite as reported in ref.[5d] Unlike lithiated 2-(chloromethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (see ref.[13]), lithiated 2-(1-chloroethyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole is quite stable at low temperatures.

[10] Under Barbier's conditions, the only two products formed were spirocyclic compounds **18b** (15% yield) and oxazetidine **19** (60% yield), easily separable by column chromatography (silica gel; petroleum ether/Et_2O, 3:2).

[11] In the case of compound **17b**, a significant cross-peak between the methyl and the hydrogen atom lying in a 1,3-relationship on the isoxazolidine ring was observed, testifying to a *cis* relationship.

[12] In the NOESY phase-sensitive spectrum of oxazetidine **19**, no cross peak was observed between the oxazetidine methyl protons and the vicinal benzylic-type proton. Moreover, as seen for diastereomeric oxazetidines **25a** and **27a** (and confirmed by their NOESY phase-sensitive spectra), a phenyl ring on the same side of an dihydrooxazolyl ring induced a shielding effect on both its geminal methylenic protons and on the two methyl groups; the latter, in particular, were shifted to high field with respect to the *tert*-butyl protons. Analogously, in the case of oxazetidine **19**, a downfield shift (ca. 0.3 ppm) observed for the two dihydrooxazolyl methyl protons with respect to the *tert*-butyl protons confirms the (3*R**,4*S**) geometry as that depicted in Scheme 6 for this compound.

[13] Lithiated 2-chloromethyl derivative **2e** tends to convert into (*E*)-1,2-bis(dihydrooxazolyl)ethene and *trans*-1,2,3-tris(dihydrooxazolyl)cyclopropane, as reported in: V. Capriati, S. Florio, R. Luisi, M. T. Rocchetti, *J. Org. Chem.* **2002**, *67*, 759−763. The addition to nitrone was therefore performed under Barbier's conditions, the mixture of 2-(chloromethyl)-4,5-dihydro-1,3-oxazole **1e** and nitrone **3a** being added to the LDA solution.

[14] The relative configurations were assigned to compounds **21-H, 22-H, 25a**, and **27a** on the basis of their NOESY phase-sensitive spectra. In the cases of **22-H** and **27a** (*cis* isomers) cross peaks were seen between the two vicinal isoxazolidine ($^3J_{H,H}$ = 10.7 Hz) and oxazetidine ($^3J_{H,H}$ = 10.0 Hz) ring hydrogen atoms, and also, for **22-H**, two additional cross peaks between H_a and the two geminal oxazolidinyl ring hydrogen atoms. In the cases of **21-H** (*trans* isomer; $^3J_{H,H}$ = 7.0 Hz) and **25a** (*trans* isomer; $^3J_{H,H}$ = 8.2 Hz), none of these cross-peaks were observed.

[15] The small ($^3J_{H,H}$ = 4.3 Hz) and the large ($^3J_{H,H}$ = 10.3 Hz) coupling constants found for **23-H** and **24-H**, respectively, as well as the absence of NOEs for the latter, are indicative of a *gauche* and a *anti* arrangement of the two vicinal protons in the two staggered rotamers (see: N. Matsumori, D. Kaneno, M. Murata, H. Nakamura, K. Tachibana, *J. Org. Chem.* **1999**, *64*, 866−876), also favoured by possible intramolecular hydrogen bonding between the OH group and the dihydrooxazolyl nitrogen atom.

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