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Synthesis of Enantiomerically Enriched Oxazolinyl[1,2]Oxazetidines

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Abstract: The first stereoselective synthesis of oxazolinyl-[1,2]oxazetidines based on the reaction of lithiated 2-(1-chloroethyl)-2-oxazolines with nitrones is described. Highly enantioenriched oxazolinyl[1,2]oxazetidines have also been prepared starting from a 1:1 diastereomeric mixture of optically active 2-(1-chloroethyl)-2-oxazolines.

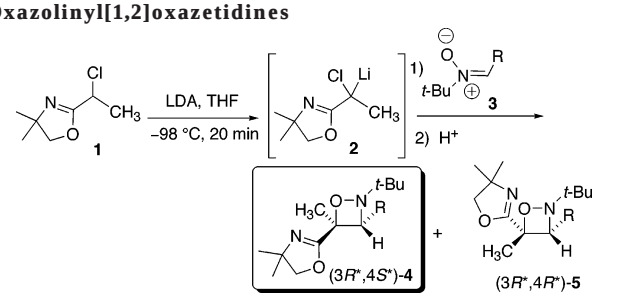
Highly strained molecules such as small cyclic compounds have interested chemists ever since the end of the nineteenth century. Synthesis, reactivity, structural features, and spectroscopic properties have been thoroughly investigated. Only few theoretical and spectroscopic studies on four-membered ring heterocycles belonging to the family of 1,2- and 1,3-oxazetidines have been reported so far.[1] The chemistry as well as synthetic procedures to oxazetidines have been rather recently reviewed.[2] The importance for this kind of heterocycles is ascribed to their strain features, which make them available to synthetic elaboration and of interest for theoretical and spectroscopic studies.

We have recently reported that lithiated 2-alkyl-2-oxazolines add to nitrones to furnish highly stereoselective *cis*- and *trans*-2-alkenyl-2-oxazolines.[3] A further investigation directed to the elucidation of the reaction mechanism provided us with evidence that under appropriate experimental conditions one can prepare 1,6-dioxa-2,9-diazaspiro[4,4]nonanes, isoxazolidin-5-ones, and some oxazolinyl[1,2]oxazetidines.[4]

In this paper, we report an unprecedented and efficient stereoselective synthesis of oxazolinyl[1,2]oxazetidines based on the addition of easily available lithiated 2-(1-chloroethyl)-2-oxazolines to nitrones. The choice for lithiated 2-(1-chloroethyl)-2-oxazolines was driven by their carbenoidic character,[5] a nucleophile and an electrophile at the same time, that makes them potential precursors to oxazetidines.

Lithiation of 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline **1** with LDA at −98 °C in THF generated lithio derivative **2**, which proved to be quite stable as previously reported.[6] The addition of α-phenylnitrone **3a** followed by quenching with saturated aqueous NH_4Cl after 3 h resulted in the formation of the *R**,*S** oxazolinyl[1,2]oxazetidines **4a** in good yield (75%) together with a small amount of the *R**,*R** isomer **5a**.[7] Reaction with aromatic nitrones **3b**,**c** gave quite good yields of oxazolinyl[1,2]oxazetidines **4b**,**c** highly stereoselectively (Table 1). In the case of the reaction with the nitrone **3d**, an appreciable amount of the diastereomeric oxazolinyl[1,2]oxazetidine **5d** was isolated.

TABLE 1. Stereoselective Synthesis of Oxazolinyl[1,2]oxazetidines



R	nitrone **3**	oxazetidine **4** (% yield)[a]	oxazetidine **5** (% yield)	ratio **4**/**5** (*R**,*S**)/(*R**,*R**)[c]
Ph	**3a**	**4a** (75)	**5a**[b]	90/10
p-$CF_3C_6H_4$	**3b**	**4b** (60)	**5b**[b]	>98/2
p-$MeOC_6H_4$	**3c**	**4c** (85)	**5c**[b]	>98/2
p-ClC_6H_4	**3d**	**4d** (48)	**5d** (32)[a]	60/40

[a] Isolated yields. [b] Oxazetidines **5a**−**c** were not isolated. [c] Diastereomeric ratio calculated on the basis of ^{1}H NMR spectroscopy of the crude reaction mixture.

No reaction took place when lithiated species **2** was treated with the nitrone **3e** (Scheme 1): the alkenyloxazoline **6** was the only product isolated in this case.[8] Therefore, it seems like as the oxazetidines formation is limited to aromatic nitrones.

In a previous paper,[4] we reported that oxazolinyl[1,2]-oxazetidines can derive from a sort of ring contraction involving spirocyclic compounds. An investigation on the reaction mechanism, using nitrone **3d**, revealed that quenching the reaction mixture at shorter reaction times (10 min) furnished the spirocyclic precursor **7** and oxazolinyl[1,2]oxazetidine **4d** (Scheme 2).

Spirocyclic compound **7** was isolated and, upon treatment with LDA, was converted into the corresponding oxazolinyl[1,2]oxazetidine **5d** proving the reaction stereospecificity (Scheme 3).[9]

The *R**,*S** and *R**,*R** relative configuration of the oxazetidines **4** and **5** could be assigned either by NOESY experiments or by ^{13}C NMR spectroscopy on the basis of the long-range coupling constants $^3J_{CH}$ between the hydrogen and the methyl group on the oxazetidine ring.[10]

Considering the high diastereoselectivity of the addition reaction of nitrones to lithiated 2-(1-chloroethyl)-2-oxazoline **2**, it was almost obvious at this stage that the

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(1) (a) Readio, J. D. *J. Org. Chem.* **1970**, *35*, 1607−1611. (b) Magers, D. H.; Davis, S. R. *THEOCHEM* **1999**, *487*, 205−210.

(2) Snider, B. B.; Duvall, J. R. *Tetrahedron Lett.* **2003**, *44*, 3067−3070.

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(7) Oxazolinyl[1,2]oxazetidine **5a** could not been isolated; it was detected by ^{1}H NMR spectroscopy in the crude reaction mixture.

(8) The alkenyloxazoline **6** was assigned the *E* configuration by analogy to what was reported in the case of similar alkenyloxazolines (see ref 4).

(9) The relative configuration of the spirocyclic compound **7** was simply ascertained by a NOESY experiment.

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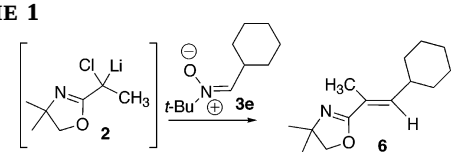
SCHEME 1



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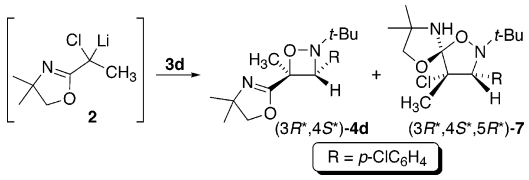

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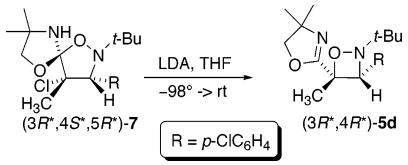
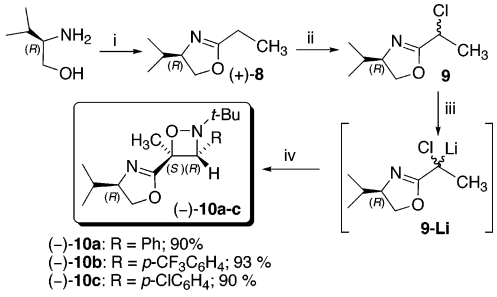
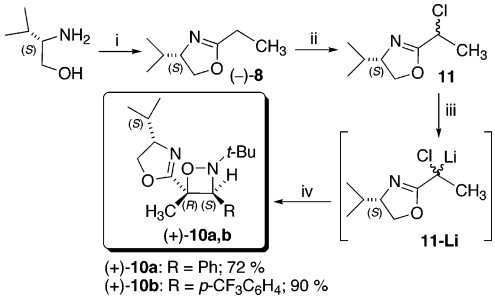


SCHEME 4[a]



[a] Key: (i) $C_2H_5C(OEt)_3$, $(CH_2)_2Cl_2$, 70 °C; (ii) *t*-BuOCl, CH_2Cl_2, 0 °C; (iii) LDA −98 °C, 20 min; (iv) nitrone **3**; −98 °C → rt.

SCHEME 5[a]



[a] Key: (i) $C_2H_5C(OEt)_3$, $(CH_2)_2Cl_2$, 70 °C; (ii) *t*-BuOCl, CH_2Cl_2, 0 °C; (iii) LDA −98 °C, 20 min; (iv) nitrone **3**; −98 °C → rt.

chiral version of such a reaction had to be tested. There were alternative routes worth of investigation among which the one based on the use of a chiral oxazoline derivative and the other one based on the use of a chiral nitrone. We decided to use a chiral 2-(1-chloroethyl)-2-oxazoline. Examples of asymmetric addition of chiral nucleophiles to nitrones have been reported.[11]

The (4*R*)-2-ethyl-4-isopropyl-2-oxazoline (+)-**8** was prepared from D-valinol and triethyl orthopropionate.[12] Chlorination of (+)-**8** with *tert*-butyl hypochlorite, according to a known procedure,[13] gave an almost 1:1 diastereomeric mixture of the correspondig 2-(1-chloroethyl)-2-oxazoline **9**. All attempts to separate such a diastereomeric mixture failed, so we decided to use it as such. Lithiation of (4*R*,1′*S*)/(4*R*,1′*R*)-**9** with LDA, followed by the addition of nitrone **3a**, afforded the oxazolinyl-[1,2]oxazetidine (−)-**10a** in a high yield (90%) and excellent stereoselectivity (dr > 95/5, ee > 96%, $[\alpha]_D = -15$) (Scheme 4).

Equally very high yield and stereoselective were the reactions of (4*R*,1′*S*)/(4*R*,1′*R*)-**9** with the nitrones **3b** and **3d,** giving oxazetidines (−)-**10b** and (−)-**10c**, respectively.

In the case of (−)-**10c**, an X-ray analysis allowed the determination of the absolute configuration at the newly created stereogenic centers (see the Supporting Information).[14]

Next, we studied the reaction of the 2-(1-chloroethyl)-2-oxazoline **11** (Scheme 5). Oxazoline (4*S*,1′*S*)/(4*S*,1′*R*)-**11** was similarly prepared as a 1:1 mixture of diastereomers from L-valinol by the same procedure used for the synthesis of **9**. The addition of nitrone **3a** to the lithiated oxazoline **11-Li**, generated by lithiation of **11**, produced the oxazolinyl[1,2]oxazetidine (+)-**10a** [the optical antipode of (−)-**10a** as ascertained by ^1H and ^{13}C NMR spectroscopy and its optical rotation] in an excellent yield and stereoselectivity (dr > 95/5, ee > 96%, $[\alpha]_D = +13$). Similarly, oxazetidine (+)-**10b**, obtained by reacting the lithiated species **11-Li** with nitrone **3b**, was proved to be the enantiomer of oxazetidine (−)-**10b**.

The ee value of oxazetidines (+)-**10a**,**b** and (−)-**10a**−**c** could be determined by ^1H NMR spectroscopy using the chiral solvating agent (CSA) (*R*)-(−)-1-phenyl-2,2,2-trifluoroethanol.[15]

It is interesting and quite intriguing that the reactions of a diastereomeric mixture of lithiated 2-(1-chloroethyl)-2-oxazolines (4*R*,1′*S*)/(4*R*,1′*R*)-**9** and (4*S*,1′*S*)/(4*S*,1′*R*)-**11** with nitrones occur so highly stereoselectively and enantioselectively.

The explanation for the observed diastereo- and enantioselectivity of the reactions of **9** and **11** with nitrones likely resides in the structural feature of the corresponding lithiated species. As similarly reported for **2**,[6] **9-Li**, and **11-Li** likely exist as azaenolates preferentially *E* configurated due to the internal chelation involving the

(10) By analogy to what was reported in the case of three-membered rings (see: Kingsbury, C. A.; Durham, D. L.; Hutton, R. *J. Org. Chem.* **1978**, *43*, 4696−4700), the *R**,*S** isomers **4a**−**d** having a trans relationship between the hydrogen and the methyl group and whose relative configurations were previously ascertained by NOESY experiments showed a smaller $^3J_{CH}$ coupling constant (in the range 2.8−3.3 Hz) with respect to **5d** (5.7 Hz) having both these groups in cis, thus validating this spectroscopic relationship also in the case of this kind of heterocycles.

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(12) Kamata, K.; Agata, I.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 3113−3116.

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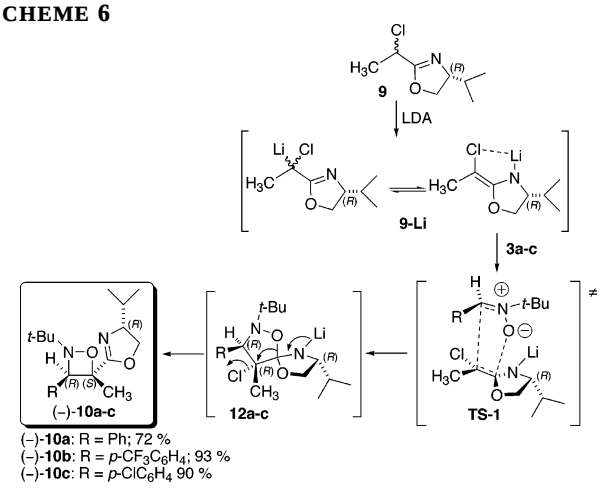
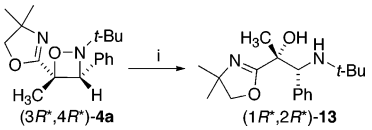
(14) CCDC-215912 contains the supplementary crystallographic data for compound (−)-**10c**. These data can be obtained free of charge at www.ccdc.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Fax: (int) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk.

(15) Following a reported experimental procedure (see: Pirkle, W. H.; Rinaldi, P. L. *J. Org. Chem.* **1977**, *42*, 3217−3219) applied to *N*-*tert*-butyloxaziridines, racemic oxazolinyl[1,2]oxazetidines **10a**−**c** (prepared starting from racemic valinol) were found to split in the presence of the above-cited CSA in correspondence of the *t*-Bu group and the oxazetidine ring hydrogen. The ee values found were >96%.

SCHEME 6



SCHEME 7[a]



[a] Key: (i) H_2/Pd/C, MeOH, 20 bar.

chlorine atom and the lithium ion. As shown in Scheme 6, the azaenolate (*E*)-**9-Li** would be attacked by the nitrones **3a**−**c** preferentially on its *si* face (the less sterically hindered diastereoface) via the transition state **TS-1** to give, through the corresponding lithiated spirocyclic compounds **12a**−**c**, the diastereo- and enantioenriched oxazolinyl[1,2]oxazetidines (−)-**10a**−**c**.

We also found that the reaction of **11** (dr 1:1) with carbonyl compounds such as benzaldehyde, performed for comparison sake, led to the formation of a mixture of the four possible diastereomers (dr 32:28:26:14, by GC−MS).[16] The explanation for the so different sterochemical outcome of the reactions of the 2-(1-chloroethyl)-2-oxazoline **11** with nitrones **3a**−**d** and with PhCHO likely resides in the features of the involved transition states. More work, however, is needed and ab initio calculations could also be helpful to this end.

In conclusion, this work reports the first stereoselective synthesis of functionalized [1,2]oxazetidines which are new and useful intermediates in organic synthesis. Indeed, oxazetidines such as **4** and **10** are masked forms of α-hydroxy-*β*-amino acids which could be freed by reduction of the N−O bond and hydrolysis of the oxazoline moiety. With regard to this, we report here that oxazetidine **4a** can be transformed into the corresponding oxazolinyl-*β*-amino alcohol **13** (98%) upon reduction with H_2 (20 bar) on Pd/C (10 wt. %) (Scheme 7).

Experimental Section

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. 2-(1-Chloroethyl)-2-oxazolines **1**, **9,** and **11**[13] and chiral nonracemic (+)/(−)-**8**[17] were prepared starting from the corresponding commercially available amino alcohols. Nitrones **3a**−**d** were prepared accordingly to reported procedures.[18] All other chemicals were of commercial grade and used without further purification. Petroleum ether refers to the 40−60 °C boiling fraction. A commercial solution of *n*-BuLi (2.5 M solution in hexanes) was titrated by using *N*-pivaloyl-*o*-toluidine prior to use.[19] For the ^{1}H and ^{13}C NMR spectra (^{1}H NMR 300, 500 MHz; ^{13}C NMR 75.4, 125 MHz), $CDCl_3$ was used as the solvent. GC−MS spectrometry analyses were performed on a gas chromatograph HP 6890 plus (dimethylsilicon capillary column, 30 m, 0.25 mm i.d.) equipped with a 5973 mass selective detector operating at 70 eV (EI). MS-ESI analyses were performed on Agilent 1100 LC/MSD trap system VL. Melting points were uncorrected. TLC was performed on Merck silica gel plates with F-254 indicator; visualization was accomplished by UV light (254 nm) or by exposing to I_2 vapor. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

(4*R*,1′*S*)/(4*R*,1′*R*)-2-(1-Chloroethyl)-4,5-dihydro-4-isopropyl-1,3-oxazole (9). Oil, 85%. Inseparable mixture of two diastereoisomers (dr 1:1). ^{1}H NMR (500 MHz): δ 0.80 (d, J = 6.7 Hz, 3 H), 0.81 (d, J = 6.7 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H), 0.89 (d, J = 6.7 Hz, 3 H), 1.66 (d, J = 6.7 Hz, 3 H), 1.67 (d, J = 6.7 Hz, 3 H), 1.69−1.76 (m, 2 H), 3.85−3.95 (m, 2 H), 3.98−4.04 (m, 2 H), 4.22−4.30 (m, 2 H), 4.50−4.58 (m, 2 H). ^{13}C NMR (125 MHz): δ 17.6, 17.8, 18.4$_0$, 18.4$_6$, 22.0, 32.2, 32.6, 48.7, 70.6, 70.7, 71.8, 71.9, 165.4. GC MS (70 eV): *m*/*z* 175 [M$^+$] (1), 132 (100) 104 (45), 96 (33). FT-IR (film) cm^{-1}: 2962, 1667 (C=N), 1447, 1376, 1079, 989, 707.

General Procedure for the Preparation of Oxazolinyl-[1,2]oxazetidines. A solution of 2-(1-chloroethyl)-2-oxazoline **1** (or **9**, or **11**, 1.0 mmol) in 2.0 mL of THF was added dropwise under N_2 to a precooled (−98 °C with a methanol/liquid nitrogen bath) solution of LDA (1.2 mmol) in dry THF (5 mL), and the resulting mixture was stirred at this temperature for 20 min. After this time, a solution of nitrone **3** (0.90 mmol) in 2.0 mL of THF was added dropwise at −98 °C; the reaction mixture was warmed to rt (3 h), quenched with saturated aqueous NH_4Cl, poured into 20 mL of saturated brine, extracted with Et_2O (3 × 10 mL), dried (Na_2SO_4); and the solvent evaporated under reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt = 8−9:2−1) to give oxazolinyl-[1,2]oxazetidines with the following data.

(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 (4a).** Spectroscopic data have been previously reported.[4]

(3*R,4*S**)-2-[2-*tert*-Butyl-4-methyl-3-(4-trifluoromethylphenyl)[1,2]oxazetidin-4-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (4b).** White solid. Mp: 92−93 °C (hexane), 60%. ^{1}H NMR (300 MHz): δ = 1.27 (s, 9 H), 1.29 (s, 3 H), 1.32 (s, 3 H), 1.35 (s, 3 H), 4.05−4.08 (2 × d, AB system, J = 9.0 Hz, 2 H), 5.54 (s, 1 H), 7.60−7.70 (m, 4 H). ^{13}C NMR (75 MHz): δ = 21.6, 23.9, 28.2, 29.8, 59.6, 65.4, 67.8, 78.1, 80.2, 124.1 (q, $^1J_{CF}$ = 273.0 Hz), 125.4 (q, $^3J_{CF}$ = 4.0 Hz), 126.2, 128.1, 130.1 (q, $^2J_{CF}$ = 32.0 Hz), 141.8, 165.4. MS (ESI) *m*/*z*: 371 [M + H]$^+$ (100). FT-IR (KBr) cm^{-1}: 2970, 1663 (C=N), 1366, 1015, 975, 836. Anal. Calcd for $C_{19}H_{25}F_3N_2O_2$: C, 61.61; H, 6.80; N, 7.56. Found: C, 61.48; H, 7.07; N, 7.47.

(3*R,4*S**)-2-[2-*tert*-Butyl-3-(4-methoxyphenyl)-4-methyl-[1,2]oxazetidin-4-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (4c).** White solid. Mp: 110−111 °C (hexane), 85%. ^{1}H NMR (300 MHz): δ = 1.08 (s, 9 H), 1.29 (s, 3 H), 1.32 (s, 3 H), 1.34 (s, 3 H), 3.81 (s, 3 H), 4.03 (s, 2 H), 5.41 (s, 1 H), 6.88−6.90 (m, 2 H), 7.46−7.48 (m, 2 H). ^{13}C NMR (75 MHz): δ = 21.4, 24.0, 28.2, 28.4, 55.4, 59.4, 65.5, 67.7, 78.5, 79.9, 113.7, 129.0, 159.3, 165.8. MS (ESI) *m*/*z*: 355 [M + Na]$^+$ (100), 333 [M + H]$^+$ (10). FT-IR (KBr) cm^{-1}: 2972, 1657 (C=N), 1514, 1365, 1250, 1090, 833. Anal. Calcd for $C_{19}H_{28}N_2O_3$: C, 68.85; H, 8.49; N, 8.43. Found: C, 68.72; H, 8.57; N, 8.27.

(16) A very poor stereoselectivity was also encountered in the reaction of lithiated optically active 2-(1-chloroethyl)-4-methoxymethyl-5-phenyl-2-oxazoline with carbonyl compounds (see ref 13).

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(3*R,4*S**)-2-[2-*tert*-Butyl-3-(4-chlorophenyl)-4-methyl-[1,2]oxazetidin-4-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (4d).** White solid. Mp: 96−98 °C (hexane), 48%. ^{1}H NMR (500 MHz): δ = 1.05 (s, 9 H), 1.24 (s, 3 H), 1.28 (s, 3 H), 1.31 (s, 3 H), 4.01 (m, 2 H), 5.42 (s, 1 H), 7.29−7.31 (m, 2 H), 7.46−7.47 (m, 2 H). ^{13}C NMR (125 MHz) δ = 21.2, 23.6, 28.1, 59.2, 65.0, 67.4, 77.8, 79.8, 128.3, 128.8, 133.4, 136.0, 165.3. MS (ESI) *m*/*z*: 337 [M + H]$^+$ (100), 359 [M + Na]$^+$ (38). FT-IR (KBr) cm^{-1}: 2977, 1655 (C=N), 1486, 1364, 1102. Anal. Calcd for $C_{18}H_{25}ClN_2O_2$: C, 64.18; H, 7.48; N, 8.32. Found: C, 64.22; H, 7.77; N, 8.17.

(3*R,4*R**)-2-[2-*tert*-Butyl-3-(4-chlorophenyl)-4-methyl-[1,2]oxazetidin-4-yl]-4,4-dimethyl-4,5-dihydro-1,3-oxazole (5d).** White solid. Mp 103−105 °C (hexane), 32%. ^{1}H NMR (500 MHz): δ = 0.76 (s, 3 H), 1.06 (s, 9 H), 1.09 (s, 3 H), 1.72 (s, 3 H), 3.52−3.57 (2 × d, AB system, J = 8.0 Hz, 2 H), 4.90 (s, 1 H), 7.24−7.25 (m, 2 H), 7.42−7.44 (m, 2 H). ^{13}C NMR (125 MHz) δ = 23.7, 24.5, 27.9, 59.0, 67.2, 70.0, 79.2, 80.3, 127.9, 128.9, 133.6, 136.0, 164.6. MS (ESI) *m*/*z*: 337 [M + H]$^+$ (100), 359 [M + Na]$^+$ (38). FT-IR (KBr) cm^{-1}: 2972, 1661 (C=N), 1489, 1365, 1192, 1089. Anal. Calcd for $C_{18}H_{25}ClN_2O_2$: C, 64.18; H, 7.48; N, 8.32. Found: C, 64.47; H, 7.74; N, 8.30.

(±)-2-(2-*tert*-Butyl-4-methyl-3-phenyl[1,2]oxazetidin-4-yl)-4-isopropyl-4,5-dihydro-1,3-oxazole (10a). White solid. Mp: 55−56 °C (hexane) 90%. ^{1}H NMR (300 MHz): δ = 0.89 (d, J = 6.7 Hz, 3 H), 0.95 (d, J = 7.3 Hz, 3 H), 1.08 (s, 9 H), 1.30 (s, 3 H), 1.79 (octet, J = 6.0 Hz, 1 H), 4.02−4.10 (m, 2 H), 4.30−4.33 (m, 1 H), 5.47 (s, 1 H), 7.32−7.35 (m, 3 H), 7.52−7.53 (m, 2 H). ^{13}C NMR (125 MHz): δ = 17.8, 17.9, 18.5, 21.4, 23.8, 32.5, 59.1, 66.0, 70.7, 71.8, 78.2, 127.5, 128.1, 137.4, 167.0. MS (ESI) *m*/*z*: 317 [M + H]$^+$. FT-IR (KBr) cm^{-1}: 2964, 1674 (C=N), 1362, 1259, 1100. Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 72.22; H, 8.77; N, 8.87.

(4*R*,3′*R*,4′*S*)-(−)-10a. 72%. $[\alpha]_D$: −15 (*c* 1, $CHCl_3$), ee > 96% ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the CSA (*R*)-(−)-2,2,2-trifluoro-1-phenylethanol, (CSA/oxazetidine molar ratio = 3/1), δ: 1.18 (major, 9 H), 1.20 (minor, 9 H), 5.55 (major, 1 H), 5.59 (minor, 1 H).

(4*S*,3′*S*,4′*R*)-(+)-10a. 90%. $[\alpha]_D$: +13 (*c* 1, $CHCl_3$), ee > 96% ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the CSA (*R*)-(−)-2,2,2-trifluoro-1-phenylethanol, (CSA/oxazetidine molar ratio = 3/1), δ: 1.18 (minor, 9 H), 1.20 (major, 9 H), 5.55 (minor, 1 H), 5.59 (major, 1 H).

(±)-2-[2-*tert*-Butyl-3-(4-trifluoromethylphenyl)-4-methyl-[1,2]oxazetidin-4-yl]-4-isopropyl-4,5-dihydro-1,3-oxazole (10b). White solid. Mp: 66−67 °C (hexane), 93%. ^{1}H NMR (500 MHz): δ = 0.80 (d, J = 6.7 Hz, 3 H), 0.86 (d, J = 6.8 Hz, 3 H), 0.99 (s, 9 H), 1.17 (s, 3 H), 1.79 (octet, J = 6.1 Hz, 1 H), 4.03−4.12 (m, 2 H), 4.33 (dd, J = 9.8, 8.5 Hz, 1 H), 5.54 (s, 1 H), 7.60−7.68 (m, 4 H). ^{13}C NMR (125 MHz): δ = 17.9, 18.4, 21.5, 23.6, 32.5, 59.2, 65.6, 70.8, 71.8, 78.0, 124.0 (q, $^1J_{CF}$ = 272.0 Hz), 125.1 (q, $^3J_{CF}$ = 3.8 Hz), 127.8, 129.8 (q, $^2J_{CF}$ = 32.0 Hz), 141.5, 166.7. MS (ESI) *m*/*z*: 407 [M + Na]$^+$ (100), 385 [M + H]$^+$ (20). FT-IR (KBr) cm^{-1}: 2965, 1679 (C=N), 1329, 1165, 1129,1096. Anal. Calcd for $C_{20}H_{27}F_3N_2O_2$: C, 62.48; H, 7.08; N, 7.29. Found: C, 62.32; H, 7.07; N, 7.17.

(4*R*,3′*R*,4′*S*)-(−)-10b. 93%. $[\alpha]_D$: −18 (*c* 1, $CHCl_3$), ee > 96% ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the CSA (*R*)-(−)-2,2,2-trifluoro-1-phenylethanol, (CSA/oxazetidine molar ratio = 3/1), δ: 1.15 (major, 9 H), 1.16 (minor, 9 H), 5.63 (major, 1 H), 5.66 (minor, 1 H).

(4*S*,3′*S*,4′*R*)-(+)-10b. 90%. $[\alpha]_D$: +22 (*c* 1, $CHCl_3$), ee > 96% ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the CSA (*R*)−(−)-2,2,2-trifluoro-1-phenylethanol, (CSA/oxazetidine molar ratio = 3/1), δ: 1.15 (minor, 9 H), 1.16 (major, 9 H), 5.63 (minor, 1 H), 5.66 (major, 1 H).

(±)-2-[2-*tert*-Butyl-3-(4-chlorophenyl)-4-methyl[1,2]-oxazetidin-4-yl]-4-isopropyl-4,5-dihydro-1,3-oxazole (10c). White solid. Mp: 98−99 °C (hexane). 55%. ^{1}H NMR (500 MHz): δ = 0.87 (d, J = 6.7 Hz, 3 H), 0.93 (d, J = 6.7 Hz, 3 H), 1.05 (s, 9 H), 1.25 (s, 3 H), 1.78 (octet, J = 6.7 Hz, 1 H), 4.03−4.09 (m, 2 H), 4.29 (dd, J = 9.1, 7.9 Hz, 1 H), 7.30−7.31 (m, 2 H), 7.46−7.48 (m, 2 H). ^{13}C NMR (125 MHz): δ = 17.9, 18.4, 21.3, 23.7, 32.4, 59.1, 65.4, 70.7, 71.8, 78.0, 128.3, 128.8, 133.4, 136.0, 166.8. MS (ESI) *m*/*z*: 373 [M + Na]$^+$ (100), 351 [M + H]$^+$ (7). FT-IR (KBr) cm^{-1}: 2966, 1679 (C=N), 1364, 1097, 966. Anal. Calcd for $C_{19}H_{27}ClN_2O_2$: C, 65.04; H, 7.76; N, 7.98. Found: C, 64.76; H, 7.73; N, 8.03.

(4*R*,3′*R*,4′*S*)-(−)-10c. 90%. $[\alpha]_D$: −2.6 (c 1, $CHCl_3$); ee > 96% ascertained by ^{1}H NMR (500 MHz, CCl_4 with $CDCl_3$ as external standard) in the presence of the CSA (*R*)-(−)-2,2,2-trifluoro-1-phenylethanol, (CSA/oxazetidine molar ratio = 3/1), δ: 1.16 (major, 9 H), 1.19 (minor, 9 H), 5.55 (major, 1 H), 5.57 (minor, 1 H).

(*E*)-2-(2-Cyclohexyl-1-methylvinyl)-4,4-dimethyl-4,5-dihydro-1,3-oxazole (6). Oil, 25%. ^{1}H NMR (300 MHz): δ = 1.06−1.50 (m, 6 H), 1.25 (s, 6 H), 1.63−1.75 (m, 5 H), 1.92−1.93 (d, J = 1.4 Hz, 3 H), 3.95 (s, 2 H), 6.23−6.26 (d, J = 9.6 Hz, 1 H). ^{13}C NMR (75 MHz): δ = 26.1, 27.3, 27.9, 28.6, 31.0, 32.6, 44.0, 46.0, 59.5, 66.4, 70.5, 122.9, 143.4, 165.4. GC MS (70 eV) *m*/*z*: 221 [M$^+$] (57), 206 (100), 140 (22), 124 (57). FT-IR (film) cm^{-1}: 2926, 1666 (C=N), 1450, 1364.

Spirocyclic compound **7** was obtained following the same general procedure just described for the preparation of oxazolinyl-[1,2]oxazetidines but quenching the reaction mixture 10 min after nitrone addition.

(3*R,3*S**,5*R**)-2-*tert*-Butyl-4-chloro-3-(4-chlorophenyl)-4,8,8-trimethyl-1,6-dioxa-2,9-diazaspiro[4,4]nonane (7).** White solid. Mp: 122−124 °C (hexane), 35%. ^{1}H NMR (300 MHz): δ = 0.98 (s, 9 H), 1.22 (s, 3 H), 1.36 (s, 3 H), 1.41 (s, 3 H), 2.20−2.50 (br. s, exchanges with D_2O, 1 H), 3.69 (d, J = 7.6 Hz, 1 H), 3.87 (d, J = 7.6 Hz, 1 H), 4.37 (s, 1 H), 6.99−7.01 (m, 1 H), 7.21−7.31 (m, 2 H), 7.84−7.86 (m, 1 H). ^{13}C NMR (75 MHz): δ = 21.5, 27.1, 27.8, 28.5, 56.6, 60.1, 70.4, 78.9, 79.2, 120.6, 127.8, 128.1, 129.2, 132.3, 133.9, 136.9. MS (ESI) *m*/*z*: 373 [M + H]$^+$ (100), 395 [M + Na]$^+$ (23). FT-IR (KBr) cm^{-1}: 2971, 1382, 1363, 1084, 1011, 873. Anal. Calcd for $C_{18}H_{26}ClN_2O_2$: C, 57.91; H, 7.02; N, 7.50. Found: C, 57.62; H, 7.31; N, 7.60.

Reduction of Oxazolinyl[1,2]Oxazetidine 4a. To a solution of **4a** (1.0 mmol) in methanol (10 mL) was added Pd on charcoal (10% w/w) and the resulting mixture hydrogenated in a "Büchi Mini Clave" apparatus at 20 bar overnight. Then the solution was filtered on Celite pad and the solvent evaporated in vacuo affording the amino alcohol **13** that was purified by crystallization from hexane.

(1*R,2*R**)-1-*tert*-Butylamino-1-phenyl-2-(4,4-dimethyl-4,5-dihydro-1,3-oxazol-2-yl)-2-propanol (13).** White solid. Mp: 83−84 °C (hexane), 98%. ^{1}H NMR (500 MHz): δ = 0.86 (s, 9 H), 1.03 (s, 3 H), 1.16 (s, 3 H), 1.23 (s, 3 H), 3.92 (s, 1 H), 3.95 (d, J = 8 Hz, 1 H), 3.98 (d, J = 8 Hz, 1 H), 7.14−7.25 (m, 5 H). ^{13}C NMR (125 MHz): δ = 23.0, 28.3, 30.4, 51.1, 62.2, 67.0, 73.9, 80.3, 127.0, 127.9, 128.3, 142.4, 169.2. MS (ESI) *m*/*z*: 305 [M + H]$^+$ (100). FT-IR (KBr) cm^{-1}: 3347, 3218, 2968, 1665, 1164, 1093, 712. Anal. Calcd for $C_{18}H_{28}N_2O_2$: C, 71.02; H, 9.27; N, 9.20. Found: C, 71.22; H, 9.33; N, 9.15.

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Supporting Information Available: Copy of the ^{1}H NMR spectrum of compound **6** and ORTEP view of compound (−)-**10c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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