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Oxazolinyloxiranyllithium-mediated synthesis of highly strained heterocyclic compounds

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Abstract—The addition reaction of α-lithiated oxazolinyloxiranes to nitrones has been investigated. 1,5,9-Trioxa-8,10-diazadispiro[2.0.4.3]-undecanes formed in a completely diastereoselective manner upon treatment of α-lithiated oxiranes with nitrones. The lithiation of optically active *trans* and *cis*-oxazolinyloxiranes followed by the addition of a nitrone resulted in the formation of the same dispirocyclic compound. An explanation for the observed stereoselectivity is provided.

1. Introduction

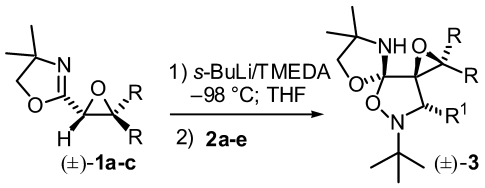
The addition of nucleophiles to nitrones to make nitrogen-containing compounds has been extensively investigated.[1,2] With reference to the carbon nucleophile addition, we have recently initiated a study dealing with the addition of lithiated 2-alkyl and α-haloalkyl-2-oxazolines to nitrones and developed a viable synthetic procedure to 2-alkenyl-2-oxazolines, 5-isoxazolidinones and oxazolinyl[1,2]oxazetidines.[3] We have also reported on the generation and synthetic utility of oxazolinyloxiranyllithiums.[4] The potential for the preparation of target molecules has also been proved.[5] In particular, in the preceding paper[6] we provided evidence that certain oxazolinyloxiranyllithiums are configurationally unstable with the consequence that the reaction with typical electrophiles takes place with no diastereoselectivity. Whatever the configuration of the starting oxirane, however, we considered it worthwhile to carry out their trapping with other electrophiles. Herein, following a preliminary communication,[7] we report on the reaction of α-lithiated oxazolinyloxiranes with nitrones.

2. Results and discussion

Lithiation of 3,3-diphenyl-2-oxazolinyloxirane **1a** was performed using *s*-BuLi/TMEDA in THF as previously reported.[8] The resulting 2-lithiooxirane **1a-Li** was reacted with the *Z-N-tert*-butyl-α-phenylnitrone[9] **2a** affording a good yield of the 7,7-dimethyl-2,2,11-triphenyl-10-*tert*-butyl-1,5,9-trioxa-8,10-diazadispiro[2.0.4.3]undecane **3a** in a completely diastereoselective manner (Table 1, Scheme 1 and Chart 1).

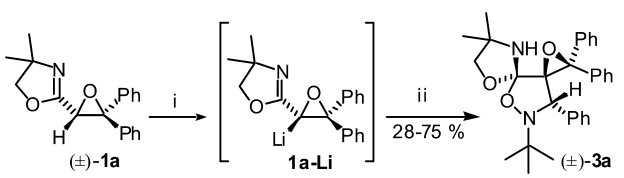
Similarly, the reaction of nitrones **2b-d** with lithiated oxazolinyloxiranes **1a-c** led to the formation of dispirocyclic compounds **3b-f**. Yields were generally good except

Table 1. Synthesis of dispirocyclic compounds **3**



Epoxide **1**	R	R^1	Nitrone	Product **3** (yield, %)[a,b]
1a	Ph	Ph	**2a**	**3a** (75)
1a	Ph	*p*-$NO_2C_6H_4$	**2b**	**3b** (28)
1b	Me	Cy	**2c**	**3c** (28)
1b	Me	*p*-ClC_6H_4	**2d**	**3d** (73)
1b	Me	*p*-$CF_3C_6H_4$	**2e**	**3e** (46)
1c	Et	*p*-ClC_6H_4	**2d**	**3f** (70)

[a] Isolated yields.
[b] Diastereomeric ratio was >98:2 as ascertained by ^1H NMR spectroscopy on the crude reaction mixture.



Scheme 1. *Conditions*: (i) *s*-BuLi/TMEDA, THF, −98°C. (ii) **2a**.

Keywords: oxazolines; oxiranes; lithiation; nitrones; spiro compounds.
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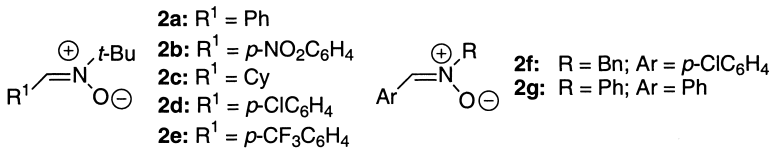


Chart 1.

with the *p*-nitrophenyl nitrone **2b** and cyclohexyl nitrone **2c** for which yields were only acceptable (Table 1).

The structural features of **3a**-**f** were spectroscopically established. In particular, the ^{13}C NMR spectra showed a typical signal at around 115–120 ppm (spiro carbon C-4) and the absence of a signal at around 165 ppm (C=N), while no absorption band at 1660 cm^{-1} (C=N stretching) was observed in the FT-IR spectra. The proposed structures were confirmed by a single crystal X-ray analysis in the case of compounds **3a** and **3d** (Fig. 1).[10]

Some useful stereochemical information could be drawn after a careful examination of the structures assigned to the novel dispirocyclic compounds **3a** and **3d**. In both these structures there is a *cis* arrangement between the oxiranyl oxygen and the nitrogen of the NH group of the oxazolidine ring and a *trans* arrangement between the oxiranyl oxygen and the aromatic group (C-11) deriving from the nitrone. Moreover, concerning the spiro carbon C-4, it can be seen that the oxygen belonging to the nitrone had attacked the C–N double bond of the oxazoline ring on its *re* face.

To explain the observed diastereoselectivity we propose a mechanism that involves a highly ordered transition state (TS-1) which originates from a concerted nucleophilic addition of the oxiranyllithium **1a**-**Li** on the *re* face of the nitrone and of the nitrone oxygen to the C–N double bond of the oxazoline ring ending up with the formation of **3a** after the acidic quenching, as outlined in Scheme 2.

The influence of the nitrone *N*-substituent was briefly investigated. While all compounds **3** derived from *N*-*tert*-butyl nitrones **2a**-**e** were stable in their spirocyclic form and formed as sole diastereomers, the product **3g** derived from the *N*-benzyl nitrone **2f** still formed stereoselectively but existed in solution as a mixture of the spiro and hydroxylamino forms depending on the solvent used as

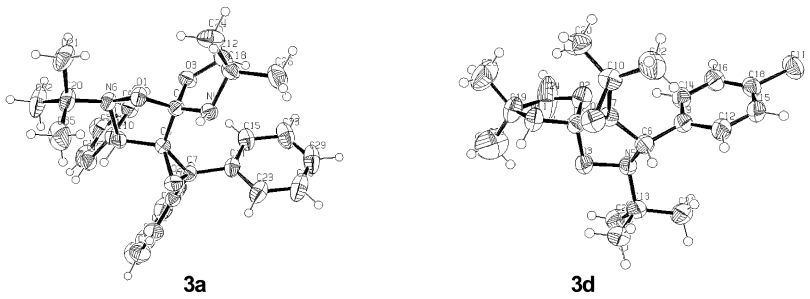
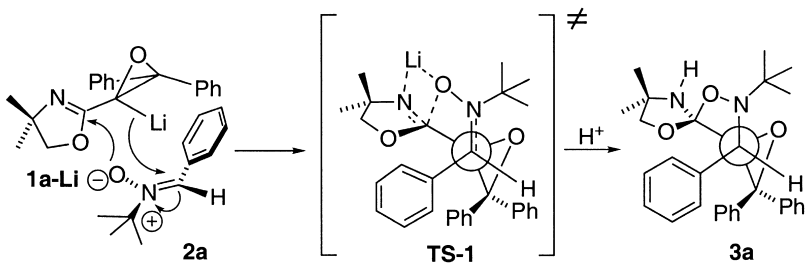
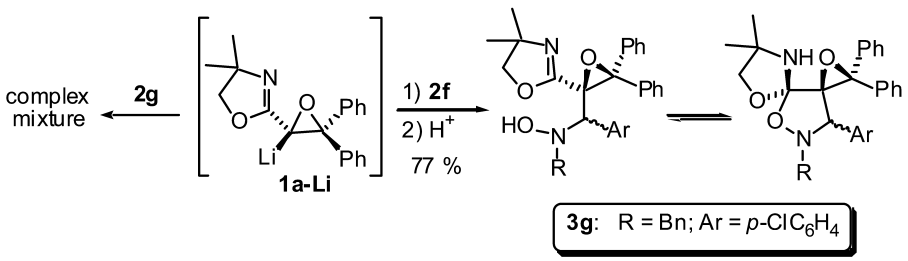


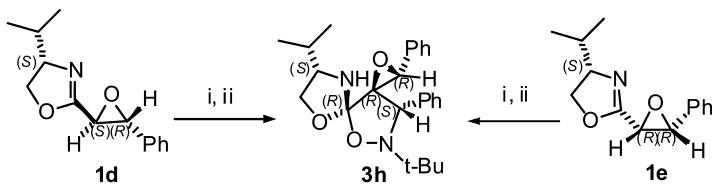
Figure 1. Ortep view of dispirocyclic compounds **3a** and **3d**.



Scheme 2.



Scheme 3.



Scheme 4. *Conditions*: (i) *s*-BuLi/TMEDA, THF, −98°C. (ii) **2a**.

shown by an IR and NMR inspection.[11] Moreover, the reaction of *N*-phenyl nitrone **2g** with **1a-Li** gave a mixture of products we were not able to identify (Scheme 3).

The diastereoselectivity of the reaction of 2-lithiooxiranes **1a-Li** with nitrones stimulated the pursuing of this work for the synthesis of optically active dispirocyclic compounds **3**. We reasoned it could be achieved using a chiral oxazolinyloxirane.

The coupling reaction of lithiated oxazolinyloxirane (4*S*,2′*S*,3′*R*) *trans*-**1d-Li**, prepared from *trans*-**1d** as reported in the preceding paper,[5a] with the nitrone **2a** resulted in the formation of the dispirocyclic compound **3h** (65% yield, dr>98:2 by ^{1}H NMR spectroscopy) (Scheme 4).

The reaction was completely diastereoselective and enantioselective: compound **3h** was isolated as one stereoisomer and showed the (2*R*,3*R*,4*R*,7*S*,11*S*) configuration as determined by an X-ray analysis (Fig. 2).[9]

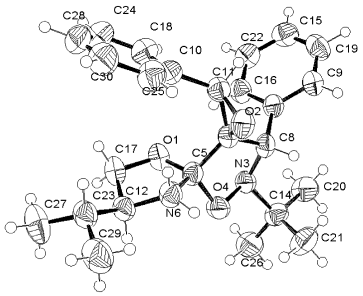
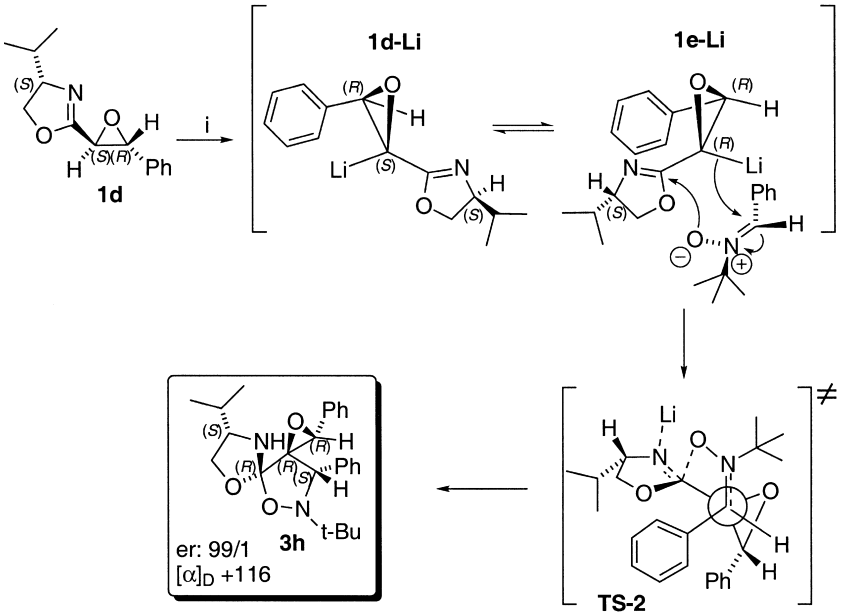


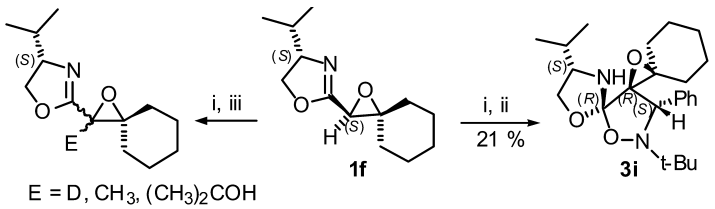
Figure 2. Ortep view of dispirocyclic compound **3h**.

Lithiated **1d** is supposed to add to the nitrone **2a** going through transition state TS-2 as illustrated in Scheme 5.[12] From a stereochemical point of view the most striking aspect of this reaction was that in the transformation **1d** to **3h** the configuration of the oxirane ring carbon atom involved in the coupling reaction underwent inversion (from *S* to *R*). To rationalize this stereochemical event we decided to study the coupling reaction of the diastereomer (4*S*,2′*R*,3′*R*) *cis*-**1e**. Lithiation of *cis*-**1e** followed by the capture of the resultant lithiated species *cis*-**1e-Li** with **2a** ended up with the formation of the same diastereomer obtained in the reaction of *trans*-**1d-Li**, that is the spirocyclic compound **3h** (Scheme 4). This reaction, therefore, occurs with retention of configuration at the oxiranyl carbon atom. We presume that there is a sort of stereoconvergency of *cis*-**1e-Li** and *trans*-**1d-Li** towards the formation of the dispirocyclic compound **3h**.

On the basis of these experimental results we came to the conclusion that there should exist a dynamic equilibrium between lithiated species *cis*-**1e-Li** and *trans*-**1d-Li** and that for steric reasons it is *cis*-**1e-Li** that adds on the *re* face of the nitrone **2a**, going through the transition state TS-2 (Scheme 5). The cyclization reaction that follows occurs, as in similar cases, on the *re* face of the C–N double bond of the oxazoline ring. Transition state TS-2, deriving from **1e-Li** and being the only one justifying the formation of the



Scheme 5. *Conditions*: (i) *s*-BuLi/TMEDA, THF, −98°C; 30 min.



Scheme 6. *Conditions*: (i) *s*-BuLi/TMEDA, THF, −98°C; 30 min; (ii) **2a**; (iii) Electrophile (D_2O, MeI, Acetone).

dispirocyclic compound **3h**, should be more favourable with respect to the other one involving **1d**-**Li** either for steric reasons in the approach of **1e**-**Li** to the nitrone (not being affected by steric hindrance between the two aryl rings and between the *t*-butyl and the *i*-propyl group) or, at the same time, owing to the presumed high reactivity of the same **1e**-**Li** compared to that of **1d**-**Li**, as reported in similar cases.[13]

It was interesting to find that lithiated epoxide **1f**-**Li**, derived from **1f**,[14] which had been found to epimerize at the α-carbon upon deuteration, reacted stereoselectively with nitrone **2a** to give spirocyclic compound **3i** as the sole diastereomer (Scheme 6).[15]

3. Conclusion

In conclusion, lithiated oxazolinyloxiranes which had been reported to react with low diastereoselectively with electrophiles such as D_2O, MeI and carbonyl compounds, react with nitrones producing highly strained dispirocyclic compounds as single diastereomers. Moreover, oxazolinyloxiranyllithiums prepared from optically pure oxazolinyloxiranes react with nitrones diastereo and enantioselectively to give almost optically pure diazadispiroundecanes which look like appropriate candidates for the elaboration to α-epoxy-β-amino acids in view of the lability of the N–O bond of the isoxazolidinyl ring and the fact that the oxazolidine moiety is a masked form of the carboxy group.

4. Experimental

4.1. General

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were freshly distilled under a nitrogen atmosphere over sodium/benzophenone ketyl. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) was distilled over finely powdered calcium hydride. Oxazolinyloxiranes **1a**-**f** were prepared as reported.[16] All other chemicals were of commercial grade and used without further purification. Petroleum ether refers to the 40–60°C boiling fraction. Commercial solutions of *n*-BuLi (2.5 M solution in hexanes) and *s*-BuLi (1.3 M solution in cyclohexane) were titrated by using *N*-pivaloyl-*o*-toluidine prior to use.[17] For ^1H and ^{13}C NMR (^1H NMR 300, 500 MHz; ^{13}C NMR 75.4, 125 MHz), $CDCl_3$ or CD_3OD were used as 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 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) or by exposing to I_2 vapour. All reactions involving air-sensitive reagents were performed under nitrogen in oven-dried glassware using syringe-septum cap technique.

4.2. Typical procedure

A solution of **1a-f** (1 mmol) and TMEDA (2.0 mmol) in 5 mL of THF at −98°C (with a methanol-liquid nitrogen bath) under N_2 was reacted with *s*-BuLi (1.5 mmol) and the resulting orange mixture was stirred for 30 min at −98°C before adding a solution of nitrone **2a-d** (1.1 mmol in 2 mL of THF). Then, the reaction mixture was warmed up to room temperature, quenched with sat. aq. NH_4Cl, poured into 20 mL of saturated brine, extracted with Et_2O (3×10 mL), dried (Na_2SO_4) and evaporated under reduced pressure. The crude mixture was flash-chromatographed (silica gel; petroleum ether/AcOEt=8–9:2–1) to give the dispirocyclic compounds **3a-i** with the following data.

4.2.1. (3*R* *,4*R* *,11*S* *)-10-*tert*-Butyl-7,7-dimethyl-2,2,11-triphenyl-1,5,9-trioxa-8,10-diazadispiro[2.0.4.3]undecane (3a). White solid (75%), mp 138–140°C (hexane), ^1H NMR (500 MHz, $CDCl_3$) δ: 0.36 (s, 3H), 1.05 (s, 9H), 1.24 (s, 3H), 2.0–2.10 (br.s, 1H, exchanges with D_2O), 3.17 (d, *J*=7.0 Hz, 1H), 3.88 (d, *J*=7.0 Hz, 1H), 3.97 (s, 1H), 6.85–6.98 (m, 7H), 7.08–7.10 (m, 2H), 7.21–7.34 (m, 4H), 7.50–7.53 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 25.4, 25.9, 29.1, 56.2, 59.0, 67.2, 69.3, 79.2, 117.7 (spiro carbon C-4), 125.8, 126.0, 126.6, 127.5, 127.6, 127.8, 127.9, 128.2, 129.0, 137.7, 138.3, 140.5. MS (ESI) *m*/*z*: 471 (100) $[M+H]^+$. FT-IR (KBr) cm^{-1}: 3359, 2979, 1448, 1379, 1216, 759, 698. Anal. calcd for $C_{30}H_{34}N_2O_3$: C, 76.57; H, 7.28; N, 5.95. Found: C, 76.97; H, 7.21; N, 6.07.

4.2.2. (3*R* *,4*R* *,11*S* *)-10-*tert*-Butyl-7,7-dimethyl-11-*p*-nitrophenyl-2,2-diphenyl-1,5,9-trioxa-8,10-diazadispiro-[2.0.4.3]undecane (3b). White solid (28%), mp 180–182°C (hexane), ^1H NMR (500 MHz, $CDCl_3$) δ: 0.33 (s, 3H), 1.02 (s, 9H), 1.22 (s, 3H), 2.0–2.10 (br.s, 1H, exchanges with D_2O), 3.23 (d, *J*=7.0 Hz, 1H), 3.87 (d, *J*=7.0 Hz, 1H), 4.04 (s, 1H), 6.80–7.10 (m, 5H), 7.20–7.40 (m, 5H) 7.45–7.55 (m, 2H), 7.75–7.85 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 25.4, 27.7, 29.1, 56.3, 59.2, 66.4, 69.0, 79.2, 80.3, 117.5 (spiro carbon C-4), 122.5, 125.7, 127.2, 127.7, 127.9, 128.1, 128.3, 129.6, 136.9, 138.0, 146.1, 148.3. FT-IR (KBr) cm^{-1}: 3351, 2976, 1519, 1346, 841, 703. Anal. calcd for $C_{30}H_{33}N_3O_5$: C, 69.88; H, 6.45; N, 8.15. Found: C, 70.02; H, 6.57; N, 7.85.

4.2.3. (5*R* *,6*R* *,14*S* *)-10-*tert*-Butyl-2,2,7,7-tetramethyl-11-cyclohexyl-1,5,9-trioxa-8,10-diazadispiro[2.0.4.3]-undecane (3c). Waxy solid (28%), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.00–1.40 (m overlapping singlets at δ 1.08, 1.15, 1.31, 1.32, 1.37, 5H) 1.08 (s, 9H), 1.15 (s, 3H), 1.31 (s, 3H), 1.32 (s, 3H), 1.37 (s, 3H), 1.50–1.80 (m, 5H) 1.85–2.05 (m, 1H), 2.20–2.30 (br.s, 1H, exchanges with D_2O), 2.91 (d, J=3.8 Hz, 1H), 3.41 (d, J=7.4 Hz, 1H), 3.86 (d, J=7.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 14.3, 19.0, 24.8, 25.5, 25.9, 26.1, 26.4, 26.6, 27.3, 28.2, 55.8, 58.1, 62.7, 64.9, 66.0, 74.0, 77.7, 120.6 (spiro carbon C-4). MS (ESI) *m*/*z*: 353 (36) $[M+1]^+$, 352 (100) $[M-1]^+$. FT-IR (KBr) cm^{-1}: 3330, 2930, 1412, 1118, 961.

4.2.4. (3*R* *,4*R* *,11*S* *)-10-*tert*-Butyl-2,2,7,7-tetramethyl-11-*p*-chlorophenyl-1,5,9-trioxa-8,10-diazadispiro[2.0.4.3]-undecane (3d). White solid (73%), mp 127–128°C (hexane), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.75 (s, 3H), 1.06 (s, 9H), 1.23 (s, 3H), 1.39 (s, 3H), 1.40 (s, 3H), 2.20–2.30 (br.s, 1H, exchanges with D_2O), 3.76 (d, J=7.7 Hz, 1H), 4.03 (s, 1H), 4.05 (d, J=7.7 Hz, 1H), 7.20–7.25 (m, 2H), 7.50–7.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.0, 24.8, 26.0, 27.9, 29.2, 56.3, 59.1, 63.4, 67.3, 76.3, 78.8, 117.3 (spiro carbon C-4), 128.3, 131.0, 132.9, 139.9. MS (ESI) *m*/*z*: 381 (100) $[M+1]^+$. FT-IR (KBr) cm^{-1}: 3392, 2963, 1461, 1050, 822.

4.2.5. (3*R* *,4*R* *,11*S* *)-10-*tert*-Butyl-2,2,7,7-tetramethyl-11-*p*-trifluoromethylphenyl-1,5,9-trioxa-8,10-diazadispiro[2.0.4.3]undecane (3e). White solid (46%), mp 81–83°C (hexane), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.73 (s, 3H), 1.07 (s, 9H), 1.23 (s, 3H), 1.40 (s, 3H), 1.42 (s, 3H), 2.20–2.30 (br.s, 1H, exchanges with D_2O), 3.77 (d, J=7.7 Hz, 1H), 4.06 (d, J=7.7 Hz, 1H), 4.11 (s, 1H), 7.50–7.57 (m, 2H), 7.65–7.73 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 18.9, 24.8, 26.0, 27.9, 29.2, 56.3, 59.3, 63.3, 67.5, 76.2, 78.8, 117.4 (spiro carbon C-4), 124.2 (q, $^1J_{CH}$=272 Hz), 125.1 (q, $^3J_{CH}$=4 Hz), 129.1 (q, $^2J_{CH}$=23 Hz), 129.9, 145.3. MS (ESI) *m*/*z*: 415 (100) $[M+1]^+$. FT-IR (KBr) cm^{-1}: 3354, 2969, 1324, 1128.

4.2.6. (3*R* *,4*R* *,11*S* *)-10-*tert*-Butyl-2,2-diethyl-7,7-dimethyl-11-*p*-chlorophenyl-1,5,9-trioxa-8,10-diazadispiro-[2.0.4.3]undecane (3f). White solid (70%), mp 128–130°C (hexane), ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.59 (t, J=7.3 Hz, 3H), 0.86 (t, J=7.3 Hz, 3H), 0.90–1.00 (m, 2H), 1.07 (s, 9H), 1.23 (s, 3H), 1.40 (s, 3H), 1.86 (q, J=7.3 Hz, 2H), 2.20–2.40 (br.s, 1H, exchanges with D_2O), 3.74 (d, J=7.6 Hz, 1H), 4.03 (s, 1H), 4.07 (d, J=7.6 Hz, 1H), 7.20–7.25 (m, 2H), 7.50–7.55 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 8.0, 8.7, 19.3, 25.6, 26.2, 27.6, 28.7, 55.6, 58.7, 66.8, 69.4, 78.3, 117.1 (spiro carbon C-4), 127.8, 130.7, 132.4, 139.6. MS (ESI) *m*/*z*: 409 (100) $[M+1]^+$. FT-IR (KBr) cm^{-1}: 3371, 2973, 1493, 1360, 1075, 824. Anal. calcd for $C_{22}H_{33}ClN_2O_3$: C, 64.61; H, 8.13; N, 6.85. Found: C, 64.74; H, 8.14; N, 6.87.

4.3. Reaction of lithiated oxazolinyloxirane 1a with *N*-benzylnitrone 2f

The same general procedure described for *N*-*tert*-butyl nitrones is followed. After chromatography, the compound **3g** was isolated in its hydroxylamino form equilibrating with the corresponding spirocyclic form in $CDCl_3$ solution. In the case of **3g**, the ^{1}H and ^{13}C NMR, run in CD_3OD solution, showed exclusively the signals of the hydroxylamino form.

4.3.1. 3-(*N*-Benzylhydroxylamino)-3-*p*-chlorophenyl-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-1,1-diphenyl-1,2-epoxypropane (3g). White solid (77%), mp 79–81°C (hexane), ^{1}H NMR (300 MHz, CD_3OD) δ: 0.47 (s, 3H), 1.11 (s, 3H), 3.69 (d, J=8.2 Hz, 1H), 3.77 (d, J=13.7 Hz, 1H), 3.83 (s, 1H), 3.90 (d, J=8.2 Hz, 1H), 4.35 (d, J=13.7 Hz, 1H), 6.85–6.95 (m, 2H), 7.05–7.15 (m, 2H), 7.18–7.45 (m, 2H). ^{13}C NMR (75 MHz, CD_3OD) δ: 26.2, 26.6, 61.8 65.9, 67.6, 69.9, 72.6, 79.5, 126.8, 127.1, 127.7, 127.8, 128.2, 128.4, 129.1, 129.3, 131.7, 133.1, 135.2, 136.7, 138.1, 138.5, 163.2 (C=N). FT-IR (KBr) cm^{-1}: 3444, 2966, 1662 (C=N), 1493, 1091, 703.

4.4. Preparation of optically active dispirocyclic compounds 3h,i

A solution of the oxazolinyloxirane **1d** (or **1e**) (1 mmol) and TMEDA (2.0 mmol) in 10 mL of THF at −98°C (methanol–liquid nitrogen bath) under N_2 was reacted with *s*-BuLi (1.5 mmol) and the resulting orange mixture was stirred for 30 min at this temperature before adding a solution of the nitrone **2a** (1.1 mmol in 2 mL of THF). Then, the reaction mixture was warmed up to room temperature, quenched with sat. aq. NH_4Cl, poured into saturated brine (20 mL), 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 the dispirocyclic compounds **3h**,**i** with the following data.

4.4.1. (2*R*,3*R*,4*R*,7*S*,11*S*)-(+)-10-*tert*-Butyl-7-isopropyl-2,11-diphenyl-1,5,9-trioxa-8,10-diazadispiro[2.0.4.3]-undecane (3h). White solid (65%), mp 158–161°C (hexane), α_D^{20}=+115 (*c* 1, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.51 (d, J=6.5 Hz, 3H), 0.80 (d, J=6.5 Hz, 3H), 0.7–0.9 (m, 1H), 1.04 (s, 9H), 2.00–2.40 (br.s overlapping t at δ 2.25, 1H, exchanges with D_2O), 2.25 (t, J=7.5 Hz, 1H), 2.90–3.00 (m, 2H), 3.49 (s, 1H), 3.85 (t, J=7.5 Hz, 1H), 4.13 (s, 1H), 7.15–7.65 (m, 10H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.1, 20.2, 25.5, 25.8, 26, 31.4, 61.4, 62, 62.8, 68.3, 71.1, 115.2 (spiro carbon C-4), 126.4, 127.2, 127.4, 127.5, 127.7, 128, 128.4, 128.7, 133.6, 140. MS (ESI) *m*/*z*: 409 (100) $[M+H]^+$. FT-IR (film) cm^{-1}: 2964, 1456, 1364, 1029, 745, 698.

4.4.2. 15-*tert*-Butyl-3-isopropyl-14-phenyl-1,7,16-trioxa-4,15-diazatrispiro[4.0.1.5^8.0^6.3^5]hexadecane (3i). Colorless oil (21%), α_D^{20}=−20 (*c* 1, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (d, J=6.6 Hz, 3H), 0.96 (d, J=6.6 Hz, 3H), 1.10 (s, 9H), 1.60–1.80 (m, 9H), 1.80–2.10 (m, 2H), 3.30–3.50 (m, 1H), 3.70 (t, J=7.5 Hz, 1H), 4.11 (s, 1H), 4.39 (t, J=7.5 Hz, 1H), 7.18–7.70 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 19.6, 20.3, 24.0, 24.5, 25.4, 26.2, 28.5, 32.8, 34.4, 59.5, 61.4, 67.8, 68.6, 71.1, 117.2 (spiro carbon C-5), 127.3, 128.3, 130.3, 141.5. MS (ESI) *m*/*z*: 423 (100) $[M+Na]^+$, 401 (34) $[M+H]^+$. FT-IR (film) cm^{-1}: 2960, 1455, 1363, 1093, 978, 702.

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10. CCDC 207742, CCDC 208735 and CCDC211589 contain the supplementary crystallographic data for compounds (±)-**3a-d** and (+)-**3h**. These data can be obtained free of charge via http://www.ccdc.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: +44-1223-336-033; or deposit@ccdc.cam.ac.uk).
11. Dispirocyclic compound **3g** tends to equilibrate in $CDCl_3$ solution with the corresponding hydroxylamino form; the ^{13}C NMR spectrum clearly shows signals at 119 and 163 ppm belonging to the two equilibrating species. Otherwise, only the hydroxylamino form was detected by ^{1}H and ^{13}C NMR spectroscopy in CD_3OD solution.
12. It is worth pointing out that in the case of **3h** the same stereochemical relationships outlined for dispirocyclic compounds **3a-d** between the oxiranyl oxygen, the nitrogen of the oxazolidine ring and the phenyl ring on C-5 were also established.
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14. Oxazolinyloxirane **1f** could be assigned the *S* configuration at the oxiranyl stereogenic centre by analogy to the oxazolinyl-oxiranes previously prepared by such a methodology, see Ref. 16b.
15. Dispirocyclic compound **3i** is supposed to have a (3*S*,5*R*,6*R*,14*S*) configuration. On the basis of the model proposed for the reaction of **1d-Li** with nitrone **2a** where an inversion at the oxiranyl α-carbon atom occurs, it's reasonable to assume that lithiated **1f**, in the reaction with **2a**, should invert its configuration for steric reasons as well.
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