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# 1,3-Dipolar Cycloaddition Reactions of Nitrones with Alkyl Vinyl Ethers Catalyzed by Chiral Oxazaborolidines

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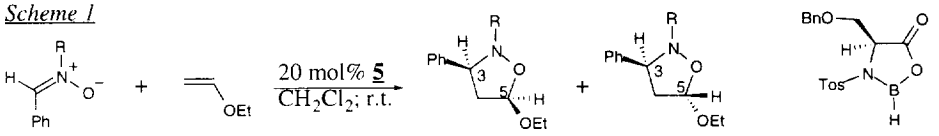
**Abstract**: The 1,3-dipolar cycloaddition reactions of various *Z*- and *E*-nitrones with ethyl vinyl ether and 2,3-dihydrofuran are catalyzed by 20 mol% of chiral oxazaborolidines at room temperature. The effect of high pressure on these reactions is discussed. © 1997 Elsevier Science Ltd.

The preparation of optically active isoxazolidines via asymmetric 1,3-dipolar cycloaddition of nitrones has been extensively utilized in the total synthesis of structurally diverse natural products[1]. Most attention has been paid to the use of chiral nitrones and chiral electron-deficient dipolarophiles. Some examples of 1,3-dipolar cycloaddition reactions of nitrones with electron-rich dipolarophiles, such as ketene O,O-dialkyl acetals[2] or alkyl vinyl ethers[3], are known from the literature. In the absence of a Lewis acid catalyst, elevated temperatures, long reaction times and a large excess of ketene acetal or vinyl ether are generally required to obtain the corresponding isoxazolidines in acceptable yields. Recently we reported the first examples of chiral Lewis acid catalyzed 1,3-dipolar cycloaddition of nitrones with ketene acetals[4]. The reactivity of nitrones toward ketene O,O-acetals was considerably enhanced by applying chiral oxazaborolidines as Lewis acid catalysts at -78 °C. The chiral Lewis acid is assumed to complex with the nitrone oxygen atom, by which the LUMO energy of the nitrone is lowered to give a $LUMO_{nitrone}$ controlled[5] enantioselective reaction with the electron-rich ketene acetals. The 1,3-dipolar cycloaddition reaction of C-phenyl-N-methyl nitrone **1** with ethyl vinyl ether **4** has been extensively studied under thermal and high pressure conditions by Dicken and DeShong[3c] (*Scheme 1*). Under the former conditions (72 h at 80 °C, without solvent) the isoxazolidine **6** was obtained as an equimolar mixture of *cis* and *trans* isomers, **6a** and **6b** respectively, in 78% yield. Application of high pressure[6] (6 h, 2 kbar, 50 °C, no solvent, 35 equiv. ethyl vinyl ether) furnished the cycloadduct in 83% chemical yield but again without any stereoselectivity (50/50 *cis/trans*).

*Scheme 1*




**1** R = Me
**2** R = Ph
**3** R = Bn

**4**

**6a** R = Me
**7a** R = Ph
**8a** R = Bn

**6b**
**7b**
**8b**

**5**

We wish to report the results of our study on the catalytic effect of chiral oxazaborolidines on the rate and stereoselectivity of 1,3-dipolar cycloaddition reactions of nitrones with alkyl vinyl ethers at normal and at high pressure. Analogous to the reaction of nitrones with ketene acetals we found that the reactions of C-

phenyl-N-alkylnitrones **1**, **2**, and **3** with ethyl vinyl ether **4** (3 equiv.) were also effectively catalyzed by 20 mol% of chiral oxazaborolidine **5** in dichloromethane at room temperature and gave complete conversion of the nitrones after 18 hours (*Scheme 1*). The absolute configuration is arbitrarily chosen. The results are presented in Table 1. The reactions were completely regioselective and the isoxazolidine products **6**[3c], **7**[3a] and **8** were isolated in 60-84% yield as mixtures of *cis* and *trans* isomers **6a/6b**, **7a/7b** and **8a/8b** which were separated by flash column chromatography on silica gel. Isolated yields were *ca.* 10% lower than the GC-yields. The isoxazolidines are stable for many years when stored at room temperature. The relative stereochemistry of the isolated *cis*- and *trans*-3-phenyl-5-ethoxy-isoxazolidines was assigned by analysis of NMR coupling constants and correlation with the known $^1$H-NMR data of *cis*-2-methyl-3-phenyl-5-ethoxy isoxazolidine **6a** and the corresponding *trans* isomer **6b**[3c]. The NMR signal multiplicities of the acetal protons H-5 of *cis*-**6a** and *trans*-**6b** were remarkably different. The *cis*-isomer displayed a doublet of doublets at δ 5.15 ppm with coupling constants of 3 and 6 Hz, whereas the *trans*-isomer showed only a doublet (J = 5 Hz) at δ 5.16 ppm. Similarly, the acetal proton H-5 in *cis*-isoxazolidine **7a** displayed a doublet of doublets at δ 5.30 ppm (J = 2.2 and 6.0 Hz), *trans*-isoxazolidine **7b** displayed a doublet at δ 5.35 ppm (J = 4.3 Hz); *cis*-isoxazolidine **8a** displayed a doublet of doublets at δ 5.17 ppm (J = 3.0 and 6.3 Hz), *trans*-isoxazolidine **8b** showed a doublet at δ 5.19 ppm (J = 4.9 Hz).

Table 1. Influence of Lewis Acid Catalyst and High Pressure on 1,3-Dipolar Cycloaddition of Nitrones **1**, **2** and **3** with Ethyl Vinyl Ether **4** at Room Temperature

| entry | nitrone | P (bar) | t (hours) | catalyst | yield (%)[a] | product | *cis/trans*[b] |
|---|---|---|---|---|---|---|---|
| 1 | **1** | 1 | 18 | **5** | 64 | **6a/6b** | 40/60 |
| 2 | | 2000 | 18 | - | 0 | - | - |
| 3 | | 2000 | 18 | **5** | 84 | **6a/6b** | 42/58 |
| 4 | **2** | 1 | 21 | **5** | 56 | **7a/7b** | 37/63 |
| 5 | | 2000 | 18 | - | 14 | **7a** | 100/0 |
| 6 | | 2000 | 19 | **5** | 60 | **7a/7b** | 38/62 |
| 7 | **3** | 1 | 21 | **5** | 80 | **8a/8b** | 40/60 |
| 8 | | 2000 | 18 | - | 0 | - | - |
| 9 | | 2000 | 19 | **5** | 65 | **8a/8b** | 40/60 |

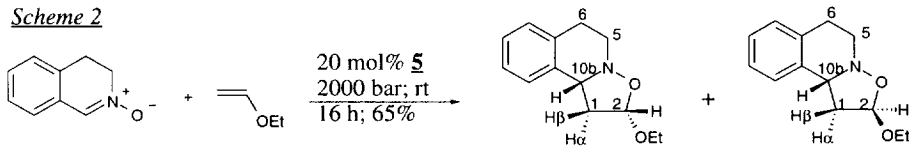
[a]The yield was determined by GC analysis of the crude reaction mixture; isolated yields after silica gel column chromatography were *ca.* 10% lower; [b] The *cis/trans* ratio was determined by GC analysis.

The results of Table 1 show that the 1,3-dipolar cycloaddition reaction does not proceed at room temperature without a catalyst. In the presence of a catalytic amount of chiral catalyst **5** the reactions proceed well at room temperature and at normal pressure. The enantioselectivities of the chiral Lewis acid catalyzed dipolar cycloadditions were determined by HPLC analysis using chiral columns. Racemic products obtained from $ZnI_2$ catalyzed cycloaddition reactions in THF were used as reference materials for determination of the enantiomeric excess. Unfortunately, in all cases the enantiomeric excesses of the *cis* and *trans* isomers are disappointingly low (*ca.* 0% ee). The dependence of the enantioselectivity on the pressure has been reported for

a catalytic asymmetric intramolecular hetero-Diels-Alder reaction[7]. However, in our case the combination of chiral catalyst and high pressure[3c] has no pronounced effect on the chemical yield or regio-, stereo- or enantioselectivity of the 1,3-dipolar cycloaddition reactions depicted in *Scheme 1*. Without a catalyst high pressure promotes the formation of the *cis* product (entry 5). This probably arises via the most crowded transition state which is expected to have the largest negative activation volume[6].

In addition to these simple acyclic *Z*-nitrones **1**, **2** and **3** we found that in the absence of a catalyst the more reactive cyclic nitrone 3,4-dihydroisoquinoline N-oxide **9** does not react with ethyl vinyl ether at room temperature in dichloromethane solution. At 2000 bar and at room temperature the reaction is very sluggish and gives the 5-ethoxy-isoxazolidine cycloadduct **10** in low yield but with good stereoselectivity (*cis*-**10a**/*trans*-**10b** = 10/90), which can be explained as described above for the cycloaddition of nitrone **2** (Table 1, entry 5). It should be noted that *exo*-addition of ethyl vinyl ether to *E*-nitrone **9** yields *trans*-isoxazolidine **10b**, while *exo*-addition to *Z*-nitrones **1**, **2** or **3** yields a *cis*-isoxazolidine **6a**[3c], **7a** or **8a**. However, at 2000 bar, in the presence of 20 mol% of chiral oxazaborolidine catalyst **5**, cyclic nitrone **9** reacts with ethyl vinyl ether at room temperature to give regioselectively the 2-ethoxy cycloadduct **10** as a mixture of *cis*- and *trans*-isomers (*cis*-**10a**/*trans*-**10b** = 33/67) in 65% yield (*Scheme 2*). Unfortunately, after testing various chiral Lewis acid catalysts we were not able to induce any significant chirality in isoxazolidine **10a** or **10b**.

*Scheme 2*

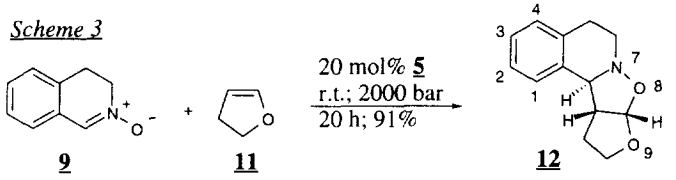



**9** **4** **10a** **10b**

The relative stereochemistry of the separated *cis*- and *trans*-isomers **10a** and **10b**, respectively, was again determined by the difference in NMR signal multiplicities for the acetal proton H-2. Now, the *trans*-isomer **10b** displayed a doublet at δ 5.26 ppm (J = 5.4 Hz) and the *cis*-isomer **10a** showed a doublet of doublets at δ 5.36 ppm (J = 3.9 and 6.6 Hz). These assignments were further confirmed by 2D-NOESY experiments. For *cis*-**10a** irradiation of H-10b and H-2 resulted in a large NOE for H-1β, and a small enhancement for H-1α. This can only be explained when H-10b, H-2 and H-1β are positioned at the same side of the isoxazolidine ring. In case of the *trans* isomer **10b** the signal of proton H-1β is only enhanced by irradiation of H-10b, whereas H-1α is mainly enhanced by H-2. In addition, for *cis*-**10a** a NOE is found for H-10b and H-2, while for *trans*-**10b** this enhancement is negligible.

The stereoselectivity of the chiral oxazaborolidine catalyzed 1,3-dipolar cycloaddition reaction of nitrone **9** was drastically improved when using 2,3-dihydrofuran **11**, a rigid *Z*-alkyl vinyl ether, as the dipolarophile (*Scheme 3*). Exclusive formation of tetracyclic *trans*-isoxazolidine **12** (53% yield after 20 hours) was observed when the reaction of nitrone **9** with 2,3-dihydrofuran **11** was catalyzed by 20 mol% $ZnI_2$ or 20 mol% chiral oxazaborolidine **5** at room temperature and ambient pressure. The yield was increased to 91% when applying high pressure (2000 bar) to these conditions. Again, no enantioselectivity was observed.

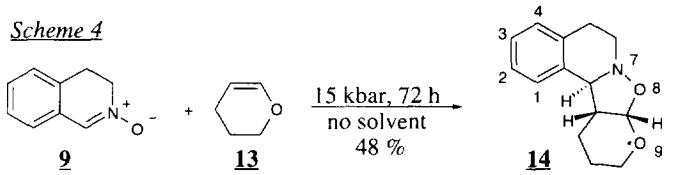
*Scheme 3*




**9** **11** **12**

The reaction of nitrone **9** with 2,3-dihydropyran **13** did not proceed in the presence of a (chiral) Lewis acid catalyst at normal pressure or at 2000 bar at room temperature. At 15 kbar, without solvent, the corresponding tetracyclic *trans*-isoxazolidine **14** was isolated in 48% yield after 3 days at room temperature (*Scheme 4*). Interestingly, Lewis acid catalysts such as $ZnI_2$ or oxazaborolidine **5** had no effect on the yield of this reaction.

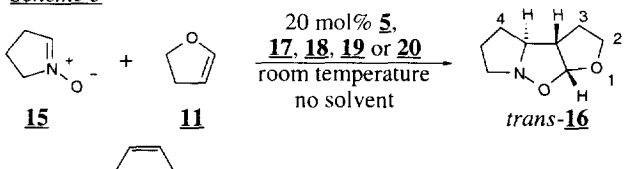
*Scheme 4*



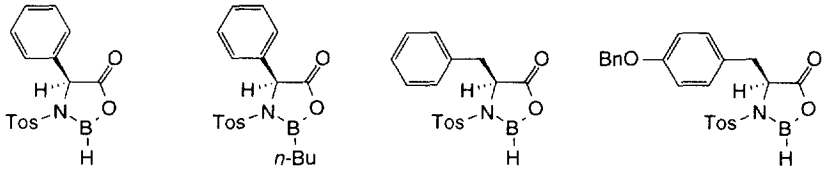

**9** **13** **14**

The scope of the (chiral) Lewis acid catalyzed *exo*-selective 1,3-dipolar cycloadditions of nitrones with cyclic *Z*-alkyl vinyl ethers was further studied with pyrroline N-oxide **15**. Kakisawa *et al.* reported that the rigid and reactive *E*-nitrone **15** undergoes an *exo*-stereoselective 1,3-dipolar cycloaddition with 2,3-dihydrofuran **11** at 140 °C to give exclusively the tricyclic *trans*-isoxazolidine **16** in high yield (*Scheme 5*)[3e]. We found that without a Lewis acid catalyst this reaction can be performed at room temperature in neat 2,3-dihydrofuran at 2000 bar to give *trans*-cycloadduct **16**. Furthermore, this reaction was catalyzed by 20 mol% $ZnI_2$ or 20 mol% chiral oxazaborolidine at room temperature and ambient pressure in neat 2,3-dihydrofuran **11** to give exclusively the *trans*-isoxazolidine **16** in good yields[8]. Some representative results are presented in Table 2.

*Scheme 5*




**15** **11** *trans*-**16**




**17** **18** **19** **20**

The effects of the position of a phenyl group in the α-amino acid side chain substituent, alkyl- or arylsubstitution of the boron atom and the arylsulfonyl nitrogen substituent of the chiral oxazaborolidine were investigated. The enantioselectivity of the related asymmetric 1,3-dipolar cycloadditions of ketene acetals with

nitrones was strongly influenced by these variations in the chiral catalyst[4]. The results in Table 2 show that highest but still modest enantioselectivity (38% ee) is obtained with N-tosyl-*L*-phenylglycine derived oxazaborolidine **17** at ambient temperature and pressure. A slight reversal of enantioselectivity (18% ee of opposite enantiomer) is achieved with the N-tosyl-*L*-phenylalanine-derived oxazaborolidine **19**. The use of *n*-butyl boron substituted oxazaborolidine **18** had no positive effect on the enantioselectivity[9]. Furthermore, a 2,4,6-trimethylphenylsulfonyl[10] or 4-nitrophenylsulfonyl nitrogen substituent[11] in **17** instead of the N-tosyl substituent had no pronounced effect on the enantioselectivity. The application of high pressure to chiral oxazaborolidine catalyzed dipolar cycloadditions of nitrone **15** does not contribute to increased enantioselectivities. Probably, the competing non-catalyzed high-pressure promoted cycloaddition lowers the enantioselectivity.

Table 2. Asymmetric 1,3-Dipolar Cycloaddition of Nitrone **15** to 2,3-Dihydrofuran **11** Catalyzed by Chiral Oxazaborolidines at Room Temperature at Normal and at High Pressure[a]

| entry | pressure (bar) | catalyst | yield (%)[b] | e.e. **16** (%)[c] |
|---|---|---|---|---|
| 1 | 1 | **5** | 65 | 0 |
| 2 | 1 | **17** | 56 | 38 |
| 3 | 1 | **18** | 74 | 34 |
| 4 | 1 | **19** | 58 | 18[d] |
| 5 | 1 | **20** | 54 | 0 |
| 6 | 2000 | - | 65 | - |
| 7 | 2000 | **5** | 69 | 4 |
| 8 | 2000 | **17** | 61 | 30 |

[a] 20 hours in 2,3-dihydrofuran **11** as solvent;[b] determined by GLC analysis; [c] determined by HPLC analysis; [d] opposite enantiomer.

It can be concluded from the results described in this paper that 1,3-dipolar cycloadditions of various nitrones with vinyl ethers are catalyzed by Lewis acids, e.g. chiral oxazaborolidines. The catalytic reactions of acyclic and cyclic nitrones with ethyl vinyl ether proceed with complete regioselectivity, but with poor stereoselectivity to give mixtures of *cis*- and *trans*-5-ethoxy-isoxazolidines. In all cases the enantioselectivity is very low. The non-catalyzed high pressure promoted reaction gives predominantly *cis* isomers. The yields have to be optimized using longer times and/or higher pressures. The chiral oxazaborolidine catalyzed *exo*-selective cycloaddition of pyrroline N-oxide with excess 2,3-dihydrofuran affords a cycloadduct with moderate enantioselectivity. This reaction opens the possibility to construct versatile chiral intermediates for pyrrolizidine alkaloids. In order to understand the factors that control the reaction and to obtain higher enantioselectivity further optimization of the reaction parameters and design of new chiral Lewis acid catalysts is needed.

## Acknowledgement

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## Experimental Section

Dichloromethane was dried and distilled from $CaH_2$. All solvents were stored over 4Å molecular sieves. All reactions were carried out under dry nitrogen or argon atmosphere. $^1$H-NMR spectra and $^{13}$C-NMR were recorded on a Varian EM 390 (90 MHz, CW), a Bruker AM-100 (100 MHz, FT) or a Bruker AM-400 (400 MHz, FT) spectrometer with TMS as internal standard. Gas chromatography was performed on a Hewlett-Packard 5710A GC-instrument equipped with a capillary HP cross-linked methyl silicone (25 m x 0.31 mm) column type PAS 017. Melting points were measured with a Reichert Thermopan microscope and are uncorrected. The high pressure apparatus operating at 1-15 kbar has been described before[12]. Enantioselectivities were determined by HPLC analysis on a LKB 2225 HPLC apparatus using Daicel CHIRALCEL OD and CHIRALPAK AD columns with hexane/2-propanol mixtures as eluents. Racemic products obtained from $ZnI_2$ catalyzed reactions were used as reference materials for determination of the enantiomeric excess by HPLC. Nitrones **1** and **2** were prepared by condensation of benzaldehyde with commercially available N-methyl-hydroxylamine and N-phenyl-hydroxylamine[13], respectively. Nitrones **3**, **9**, and **15** were prepared by oxidation of the corresponding secondary amines with $Na_2WO_4.2H_2O/H_2O_2$[3h,14]. N-arylsulphonyl *L*-α-amino acids were prepared according to literature procedures[15].

General procedure for catalyzed 1,3-dipolar cycloadditions of nitrones to ethyl vinyl ether (A)

The chiral oxazaborolidines (0.2 mmol) were prepared *in situ* at room temperature under an inert nitrogen atmosphere from N-tosyl-*L*-α-amino acids by addition of equimolar amounts of $BH_3$-THF (1M solution in THF; reaction time 10 min.) or phenyl- or *n*-butylboronic acid (in the presence of 4Å powdered molecular sieves; reaction time 30 min.) in a dry solvent (total volume 4 ml)[4]. Nitrone (1.0 mmol) was added at room temperature followed by ethyl vinyl ether (3 equiv.). The conversion of nitrone can be easily followed by GC-analysis. After the reported time (16-21 hours) the reaction mixture was quenched with saturated aqueous sodium bicarbonate, extracted twice with dichloromethane and diethyl ether, dried with sodium sulphate and concentrated *in vacuo* to give the crude 5-alkoxyisoxazolidine. The ratio of *cis*- and *trans*-isomers was determined by GC. The *cis*- and *trans*-isomers were separated by flash chromatography on silica gel using ether/*n*-hexane mixtures (1/1-4, v/v) as eluent. Isolated yields were *ca.* 10% lower than GC-yields. The enantiomeric excess was determined by chiral HPLC analysis of mixtures of *cis*- and *trans*-isomers. Samples for HPLC analysis were purified by small-scale (*ca.* 10 mg) flash chromatography on silica gel using ether/*n*-hexane mixtures as eluent.

General procedure for catalyzed 1,3-dipolar cycloadditions of nitrones to 2,3-dihydrofuran **11** (B)

The chiral oxazaborolidines (0.2 mmol) were prepared in 4 ml neat 2,3-dihydrofuran **11** as described above (A). Nitrone (1.0 mmol) was added at room temperature. After the reported time the reaction mixture was worked up as described in procedure A.

General procedure for high-pressure promoted 1,3-dipolar cycloadditions of nitrones (C)

When applying high pressure, the reaction mixture is placed into a teflon ampule flushed with dry argon. The ampule was closed and kept under pressure for the reported time. The reaction mixture was worked up as described in procedure A.

***Cis*- and *trans*-5-ethoxy-3-phenyl-N-methyl isoxazolidine 6**[3c]

Oil; all physical data were identical to those reported in the literature[3c]. HPLC analysis was performed with a Daicel Chiralcel OD column; eluent *n*-hexane/2-propanol (98/2, v/v) ; flow rate 1.0 ml/min.; UV detection at 226 nm; *cis* enantiomers **6a**: 4.71 and 8.80 min.; *trans* enantiomers **6b**: 6.77 and 9.48 min.

***Cis*- and *trans*-5-ethoxy-3-phenyl-N-phenyl isoxazolidine 7**[3a]

*Cis*-isomer **7a**: solid, m.p. 83 °C (lit.[3a] 83 °C). $^1$H-NMR (100 MHz, $CDCl_3$) δ (ppm) 1.23 3H, t, J = 7.1 Hz, $CH_2CH_3$; 2.30 1H, ddd, J = 2.2, 6.8 and 13.1 Hz, H-4; 2.96 1H, ddd, J = 6.0, 9.5 and 13.1 Hz, H-4; 3.59 1H, dq, J = 7.1 and 9.5 Hz, C*H*H-$CH_3$; 3.89 1H, dq, J = 7.1 and 9.5 Hz, CH*H*-$CH_3$; 4.24 1H, dd, J = 6.8 and 9.5 Hz, H-3; 5.30 1H, dd, J = 2.2 and 6.0 Hz, H-5; 6.83-7.44 10H, m, ArH. *Trans*-isomer **7b**: oil. $^1$H-NMR (100 MHz, $CDCl_3$) δ (ppm) 1.06 3H, t, J = 7.1 Hz, $CH_2CH_3$; 2.51 1H, ddd, J = 4.3, 10.1 and 12.1 Hz, H-4; 2.80 1H, dd, J = 7.1 and 12.1 Hz, H-4; 3.59 1H, dq, J = 7.1 and 9.5 Hz, C*H*H-$CH_3$; 3.81 1H, dq, J = 7.1 and 9.5 Hz, CH*H*-$CH_3$; 4.81 1H, dd, J = 7.1 and 10.1 Hz, H-3; 5.35 1H, d, J = 4.3 Hz, H-5; 6.89-7.46 10H, m, ArH. The enantiomeric mixture of *cis*-**7a** and *trans*-**7b** could not be separated by HPLC using Daicel Chiralcel OB, OD or Chiralpak AD columns; eluent 90/10-99/1 (v/v) *n*-hexane/2-propanol; flow rate 0.75-1.0 ml/min.; UV detection at 226 nm.

***Cis*- and *trans*-5-ethoxy-3-phenyl-N-benzyl isoxazolidine 8**

*Cis*-isomer **8a**: oil; $^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 3H, t, J = 7.1 Hz, $CH_2CH_3$; 2.31 1H, m, H-4; 2.88 1H, m, H-4; 3.47 1H, dq, J = 7.1 Hz and J = 9.3 Hz, CH*H*-$CH_3$; 3.65 2H, d, J = 14.7 Hz, $CH_2$-Ph; 3.77 1H, dq, J = 7.1 Hz and J = 9.3 Hz, C*H*H-$CH_3$; 4.02 1H, d, J = 14.8 Hz, H-3; 5.17 1H, dd, J = 3.0 Hz and J = 6.3 Hz, H-5; 7.19-7.49 10H, m, ArH. $^{13}$C-NMR δ (ppm) 15.2 ($CH_3$), 46.7 (C-4), 59.1 ($\underline{C}H_2$-$CH_3$), 63.4 ($\underline{C}H_2$-Ph), 70.4 (C-3), 100.7 (C-5), 126.8-129.6 (10 C-Ar), 137.7 ($C_{ipso}$, N-aryl), 138.6 ($C_{ipso}$, 3-phenyl). HRMS m/e (rel. int.) $C_{18}H_{21}NO_2$ : 284 (M+1, 2), 283 (M+, 12), 162 (12), 161 (96), 133 (25), 115 (3), 105 (15), 91 ($PhCH_2^+$, 100). Peak Match : Calc. 283.1572 Found : 283.1578 ± 0.0011. *Trans*-isomer **8b**: oil; $^1$H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 3H, t, J = 7.1 Hz, $CH_2CH_3$; 2.45 1H, ddd, J = 4.9, 10.2 and 12.7 Hz, H-4; 2.62 1H, dd, J = 6.4 and 12.7 Hz, H-4; 3.48 1H, dq, J = 7.1 Hz and J = 9.5 Hz, CH*H*-$CH_3$; 3.86 1H, dq, J = 7.1 and 9.5 Hz, CH*H*-$CH_3$; 4.08 2H, d, J = 2.9 Hz, $CH_2$-Ph ; 4.31 1H, dd, J = 6.4 and 10.2 Hz, H-3; 5.19 1H, d, J = 4.9 Hz, H-5; 7.19-7.44 10H, m, ArH. $^{13}$C-NMR δ (ppm) 15.2 ($CH_3$), 46.1 (C-4), 62.9 ($\underline{C}H_2$-$CH_3$), 63.6 ($\underline{C}H_2$-Ph), 67.9 (C-3), 102.5 (C-5), 127.0-129.4 (10 C-Ar), 138.0 ($C_{ipso}$, N-aryl), 140.0 ($C_{ipso}$, 3-phenyl). HRMS m/e (rel. int.) $C_{18}H_{21}NO_2$ : 284 (M+1, 3), 283 (M+, 12), 213 (4), 162 (12), 161 (95), 133 (24), 115 (4), 105 (14), 91 ($PhCH_2^+$, 100). Peak Match : Calc. 283.1572 Found : 283.15778 ± 0.00084. HPLC analysis was performed with a Daicel Chiralcel OD column; eluent 98/2 (v/v) *n*-hexane/2-propanol; flow rate 1.0 ml/min.; UV detection at 226 nm; *cis* isomers **8a** : 4.45 and 9.09 min.; *trans* isomers **8b** : 5.97 and 7.17 min.

***Cis*- and *trans*-1,5,6,10b-tetrahydro-2H-isoxazolo[3,2-a]isoquinolin-2-yl ethyl ether 10**

*Cis*-isomer **10a** : oil; $^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.18 3H, t, J = 7.1 Hz, $CH_3$; 2.35 1H, ddd, $J_{H1,H10b}$ = 10.2 Hz, $J_{H1,H2}$ = 3.9 Hz, $J_{H1,H1'}$ = 11.6 Hz, H-1; 2.78 1H, d, J = 16.3 Hz, H-1'; 2.96 1H, ddd, J = 6.6 Hz, J = 1.7 Hz, J = 9.6 Hz, H-6'; 3.06 1H, ddd, $J_{H5',H6}$ = 6.8 Hz, $J_{H5',H6'}$ = 4.7 Hz, $J_{H5',H5}$ = 11.1 Hz, H-5'; 3.39 1H, m, H-6; 3.54 2H, m, $OCH_2$ and H-5; 3.84 1H, dq, J = 7.1 Hz, J = 2.3 Hz, $OCH_2$; 4.58 1H, t, $J_{H10b,H1'}$ = 9.6 Hz, H-10b; 5.36 1H, dd, $J_{H2,H1}$ = 3.9 Hz, $J_{H2,H1'}$ = 6.6 Hz, H-2; 7.14 4H, arom.-H. $^{13}$C-NMR δ (ppm) 15.2 ($CH_3$),

29.5 ($CH_2$, C-1), 44.2 ($CH_2$, C-6), 49.9 ($CH_2$, C-5), 62.5 (C-10b), 64.0 ($CH_2O$), 106.1 (C-2), 126.2 (C-8), 126.5 (C-9), 127.5 (C-10), 133.4 (C-6a), 135.6 (C-10a). *Trans*-isomer **10b** : oil; $^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.25 3H, t, J = 7.1 Hz, $CH_3$; 2.44 1H, ddd, $J_{H1,H10b}$ = 7.4 Hz, $J_{H1,H2}$ = 5.4 Hz, $J_{H1,H1'}$ = 13.4 Hz, H-1' 2.65 1H, ddd, $J_{H1',H10b}$ = 7.4 Hz, $J_{H1',H1}$ = 13.4 Hz, $J_{H1',H2}$ = 0 Hz, H-1'; 2.88 2H, m, H-6, H-6'; 3.20 1H, ddd, $J_{H5',H6}$ = 7.5 Hz, $J_{H5',H6'}$ = 4.7 Hz, $J_{H5',H6}$ = 11.1 Hz, H-5'; 3.31 1H, ddd, $J_{H5,H6}$ = 5.4 Hz, $J_{H5,H6'}$ = 5.7 Hz $J_{H5,H5'}$ = 11.1 Hz, H-5; 3.49 1H, dq, J = 7.1 Hz, J = 2.3 Hz, $OCH_2$; 3.86 1H, dq, J = 7.1 Hz, J = 2.3 Hz, $OCH_2$; 4.76 1H, t, $J_{H10b,H1'}$ = 7.4 Hz, H-10b; 5.26 1H, d, $J_{H2,H1}$ = 5.4 Hz, H-2; 7.15 4H, arom.-H. $^{13}$C-NMR δ (ppm) 15.1 ($CH_3$), 26.8 ($CH_2$, C-1), 43.5 ($CH_2$, C-6), 49.6 ($CH_2$, C-5), 60.1 (C-10b), 63.2 ($CH_2O$), 101.6 (C-2), 126.4 (C-8), 126.4 (C-9), 128.2 (C-10), 133.8 (C-6a), 135.7 (C-10a). HRMS m/e (rel. int.) $C_{13}H_{17}NO_2$ 219 ($M^+$, 15). 174 (-OEt, 6), 148 (19), 147 (100), 130 (18), 117 (17). Peak Match : Calc. 219.2593 Found : 219.2600 ± 0.00066. In order to determine the enantiomeric excess of **10a**- and **10b**-isomers HPLC analysis was performed with a Daicel Chiralcel OD column; eluent 95/5 (v/v)*n*-hexane/2-propanol; flow rate 1.0 ml/min.; UV detection at 226 nm; *cis*-**10a** : 8.53 and 8.97 min.; *trans*-**10b** : 7.17 and 14.90 min.

***Trans*-5,8a,10,11,11a,11b-hexahydro-6H-furo[3',2':4,5]isoxazolo[3,2-a]isoquinoline 12**

Oil; $^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) 2.19-2.30 2H, m, 2xH-11; 2.54 1H, m, H-11a; 3.11-3.20 2H, m, 2xH-10; 3.29 1H, m, H-5; 3.59 1H, m, H-6; 4.03 1H, m, H-5'; 4.22 1H, m, H-6'; 4.35 1H, br s, H-11b; 5.73 1H, d, J= 5.3 Hz, H-8a; 7.08-7.26 4H, m, H-1, H-2, H-3 and H-4. $^{13}$C-NMR δ (ppm) 23.3 ($CH_2$, C-11), 32.4 ($CH_2$, C-5), 48.5 ($CH_2$, C-6), 55.5 (C-11a), 68.0 ($CH_2$, C-10), 68.6 (C-11b), 106.5 (C-8a), 126.6 (C-2 and C-3), 126.7 (C-4), 128.6 (C-1), 133.8 (C-4a), 135.5 (C-4b). HRMS m/e (rel. intensity) $C_{13}H_{15}NO_2$ 217 ($M^+$, 63), 172 (5), 148 (52), 147 (100), 130 (21), 117 (14). Peak Match : Calc. 217.1103 Found : 217.1102 ± 0.0010. HPLC analysis was performed with a Daicel Chiralcel OD column; eluent 90/10 (v/v) *n*-hexane/2-propanol; flow rate 1.0 ml/min.; UV detection at 254 nm; enantiomers at 12.80 and 18.50 min.

***Trans*-5,10,11,12,12a,12b-hexahydro-6H,8aH-pyrano[3',2':4,5]isoxazolo[3,2-a]isoquinoline 14**

The 1,3-dipolar cycloaddition reaction of nitrone **9** (1 mmol) with 2,3-dihydropyran **13** was performed at 15 kbar pressure in neat 2,3-dihydropyran following general procedure C. After 3 days the cycloadduct was isolated in 48% yield as an oil after flash chromatography on silica gel. $^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.55 1H, m, H-11; 1.93-2.09 3H, m, 2xH-12 and H-11'; 2.34 1H, m, H-12a; 2.70 1H, m, H-5; 2.93 1H, m, H-5'; 3.11 1H, m, H-10; 3.48-3.58 2H, m, H-10' and H-6; 4.04 1H, m, H-6'; 4.54 1H, d, J = 8.3 Hz, H-12b; 5.20 1H, d, J = 4.1 Hz, H-8a; 7-09-7.26 4H, m, H-1, H-2, H-3 and H-4. $^{13}$C-NMR δ (ppm) 20.6 ($CH_2$, C-12), 22.0 ($CH_2$, C-11), 25.6 ($CH_2$, C-5), 49.0 (C-12a), 51.4 ($CH_2$, C-6), 62.2 (C-12b), 63.4 ($CH_2$, C-10), 98.9 (C-8a), 126.4 (C-2 and C-3), 126.5 (C-4), 128.4 (C-1), 135.3 (C-4a), 135.7 (C-4b). HRMS m/e (rel. intensity) $C_{14}H_{17}NO_2$ 231 ($M^+$, 5), 172 (1), 148 (29), 147 (100), 130 (7), 117 (3). Peak Match : Calc. 231.1259 Found : 231.1258 ± 0.0012.

***Trans*-perhydrofuro[3,2-d]pyrrolo[1,2-b]isoxazole 16**[3e]

Oil; $^1$H-NMR (400 MHz, $CDCl_3$) δ (ppm) 1.70 2H, m, 2xH-5; 1.94-2.09 4H, m, 2xH-3 and 2xH-4; 2.95 1H, m, H-3a; 3.11 1H, dd, J = 6.0 and 7.5 Hz, NCH*H*, H-6; 3.34 1H, t, J = 8.0 Hz, NC*H*H, H-6; 3.48 1H, m, OCH*H*, H-2; 3.95 1H, m, OC*H*H, H-2; 4.13 1H, ddd, J = 6.0, 8.2 and 10.7 Hz, H-3b; 5.71 1H, d, J = 5.2 Hz, H-8a. $^{13}$C-

NMR δ (ppm) 24.0 ($CH_2$, C-5), 31.2 ($CH_2$, C-3), 32.5 ($CH_2$, C-4), 54.0 (C-3a), 57.0 ($CH_2$, C-6), 68.5 ($CH_2$, C-2), 73.7 (C-3b), 106.2 (C-8a). All $^1$H-NMR data were in full agreement with the data reported in the literature[3e]. HRMS m/e (rel. int.) $C_8H_{13}NO_2$: 156 (M+1, 1), 155 (M+, 13), 110 (5), 96 (9), 87 (5), 86 (100), 70 (9). Peak Match : Calc. 155.0946 Found : 155.0949 ± 0.00062. HPLC analysis was performed with a Daicel Chiralpak AD column; eluent 98/2 (v/v) *n*-hexane/2-propanol; flow rate 0.75 ml/min.; UV detection at 210 nm; isomers : 28.9 and 30.3 min.

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