C-[*o*-(*p*-TOLYL)SULFINYL]PHENYLNITRONES. SYNTHESIS AND REACTIVITY IN [3+2] DIPOLAR CYCLOADDITIONS

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Abstract – The synthesis of the title compounds and the results obtained in their reactions with different dipolarophiles is presented. Alkylidene malonates afford the best conversions and stereoselectivities, providing enantiomerically pure isoxazolidines easily transformed into interesting tricyclic structures with *t*-BuLi.

INTRODUCTION

Asymmetric [3+2] dipolar cycloadditions is one of the most powerful tools for the construction of enantiomerically pure five membered heterocycles.[1] Among them, isoxazolidines are mainly prepared by inter[1] or intramolecular[2] reactions of nitrones. Intermolecular processes have been reported starting from chiral dipoles[3] or dipolarophiles,[1c,1d,3,4] or using asymmetric catalysis.[5,6] The sulfinyl group has been used for controlling the stereochemistry of many reactions involving nitrones, but in most of cases it is located at the dipolarophile,[7] with only three precedents when it is located at the nitrone.[8] In the course of our research program devoted to asymmetric cycloadditions mediated on sulfoxides,[9] we were interested in the preparation of C-arylnitrones bearing a *p*-tolylsulfinyl group at *o*-position, and the study of their cycloadition reactions, because 2-(*p*-tolylsulfinyl)benzyl fragment had provided excellent results in many other asymmetric processes previously studied.[10,11] Results obtained in this study are here reported.

RESULTS AND DISCUSSION

Enantiomerically pure starting aldehyde **1**, used for the synthesis of nitrones **2-5**, was prepared following the procedure reported,[12] as indicated in Scheme 1.
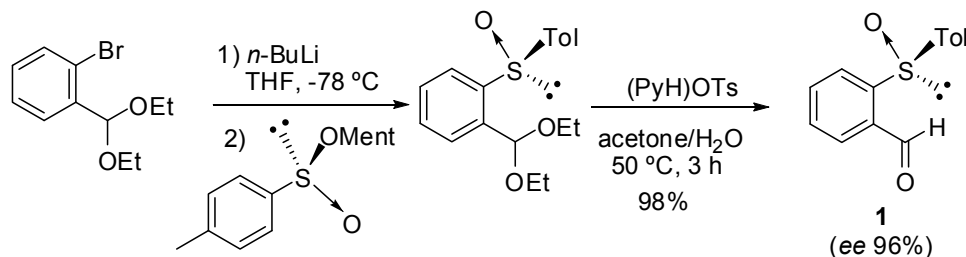
Scheme 1

Condensation of **1** with *N*-alkylhydroxylamine hydrochloride or *N*-phenylhydroxylamine in the presence of Na$_2$CO$_3$ as base and molecular sieve or MgSO$_4$, yielded the nitrones **2-5** (Scheme 2). Compounds **2** and **3** are obtained at room temperature with very high or quantitative yields. Reaction with *N*-phenylhydroxylamine is slower at room temperature, being so it was needed to heat at 50 °C to obtain better results of **4** (65% yield in 1 day). *N-t*-butylhydroxylamine is even less reactive and the yield of **5** is only 10% after 3 days. These results indicate that condensation is sensitive to the steric effects.
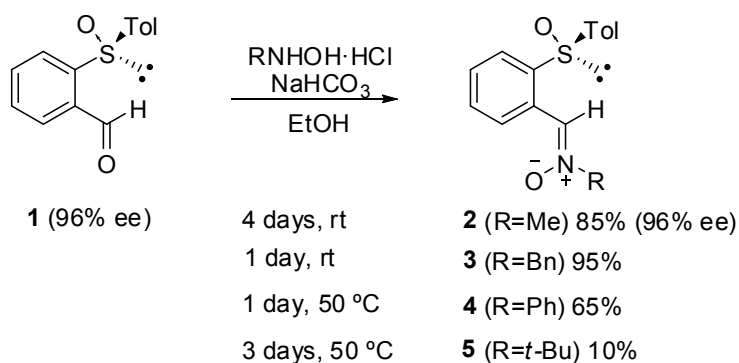
Scheme 2

The enantiomeric excess of **2**, determined by chiral HPLC, resulted to be identical to that of the starting aldehyde, which indicates that reaction conditions used for preparing nitrones do not affect the optical purity of the sulfinyl centre. The structure of **2**, determined by X-ray diffraction studies (Figure 1),[13] shows the *Re*-face of the nitrone carbon hindered by the tolyl ring joined to the sulfinyl group, thus predicting a high diastereofacial selectivity in the approaches of the different reagents.

Reactions with olefins bearing alkyl or alkoxy groups (electron-rich double bonds) were unsuccessful. Cyclohexene and 1-hexene do not react with **2** after 6 days in refluxing toluene. The formation of isoxazolidines could be detected by NMR of the reaction mixtures of **2** with styrene, but they could not be isolated as pure compounds.
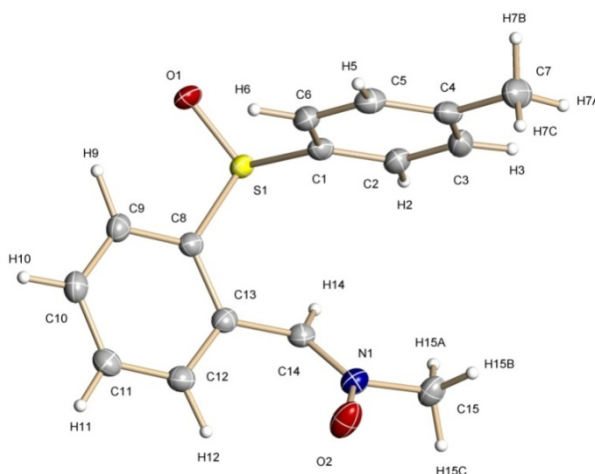
Figure 1

The reaction of **2** with ethyl vinyl ether affords, after 6 days at 110 ºC, a 3:1 mixture of isoxazolidines. Under these conditions conversion was not complete (see Scheme 3) and the aldehyde **1**, resulting in the hydrolysis of **2**, was also detected. Separation of adducts was not possible in our hands. We repeated the reaction at 50 ºC looking for a higher selectivity that made possible the isolation and characterization of the major isoxazolidine. However, the conversion was very low after 6 days and only traces of the cycloadducts were detected.
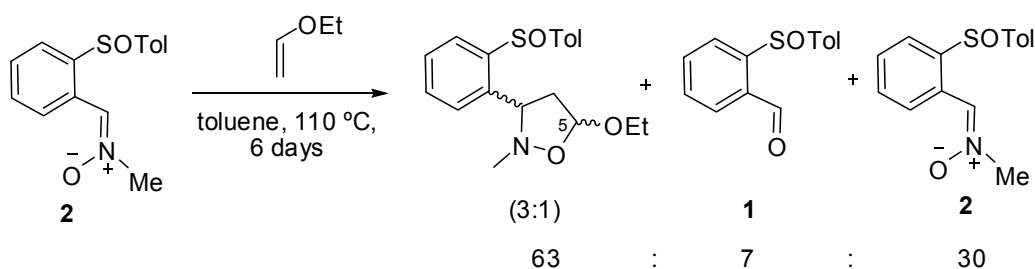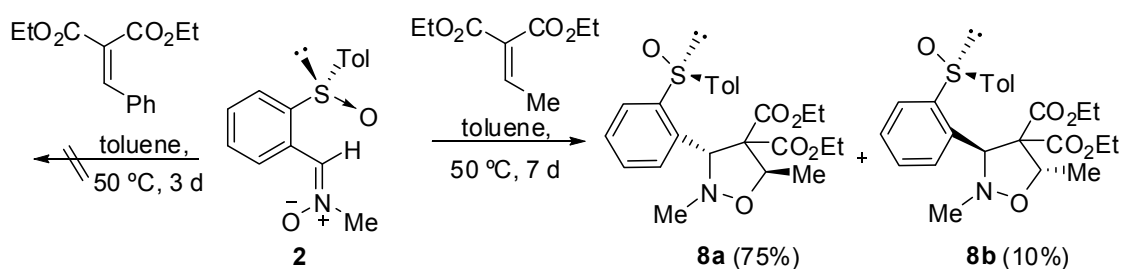

Scheme 3

Electron poor olefins bearing only one electron-withdrawing group (EWG) provided poor results of stereoselectivity. Reaction of **2** with methyl vinyl ketone (excess) at 50 ºC for 3 days afforded complex crude mixture of products containing polymerization products and a 1:1 mixture of isoxazolidines whose separation was not possible. Under these conditions reaction of **2** with pent-3-en-2-one (excess), with lower tendency to polymerization, afforded a mixture in which the major components were **6a** and **6b** (1:1), that were isolated in 80% combined yield (Scheme 4). After separation by column chromatography, the relative stereochemistry of **6a** and **6b** was determined as (*r*-4,*c*-3,*t*-5) by NOESY experiments. The absolute configuration of these compounds could not be assigned.
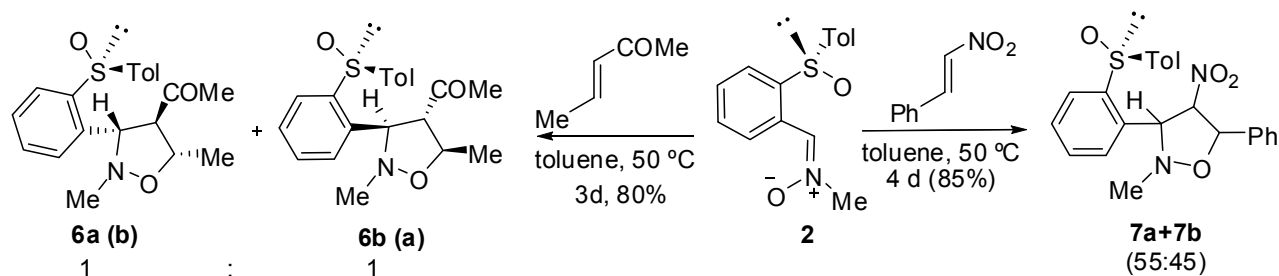
Scheme 4

A similar result was obtained from (*E*)-2-nitrostyrene (Scheme 4) which afforded a mixture of isoxazolidines **7a** and **7b** in 85% combined yield. Despite their separation was not possible, their structure and regiochemistry could be established from the NMR spectra of the mixture. Other nitroalkenes and vinyl sulfones were studied but the results were always unsuccessful.

The best results were obtained in reactions of nitrones with olefins gem-disubstituted by electron-withdrawing groups, and of special interest are the reactions with diethyl ethylidenemalonate because there are not many results in the literature concerning their reactions with nitrones.[14] Reaction of nitrone **2** with diethyl ethylidenemalonate for 7 days in toluene at 50 ºC afforded a 83:17 mixture of isoxazolidines **8a** and **8b** (Scheme 5), which were separated by column chromatography and isolated with 85% of combined yield.

Scheme 5

The use of higher temperatures reduces the reaction time but also the stereoselectivity, whereas the change of the solvent (CH$_2$Cl$_2$ instead of toluene) has not significant consequences in reactivity nor selectivity. Under the same conditions diethyl benzylidene malonates did not react. Despite the low reactivity of this dipolarophile with *N*-methyl α-phenylnitrone had been reported,[4c] we cannot discard that the different behavior of benzylidene and ethylidene malonates could be due to the easier cycloreversion of the first one due to the stabilization of the double bond exerted by the phenyl group.

The absolute configuration of the major isoxazolidine **8a** has been unequivocally established by X-ray diffraction studies.[13] NOESY experiments allowed establishing the *trans* relationship of the aryl (at C-3)

and methyl (at C-5) in both diastereoisomers. As we know the absolute configuration of **8a** (Figure 2), that of **8b** should be that shown in Scheme 5.
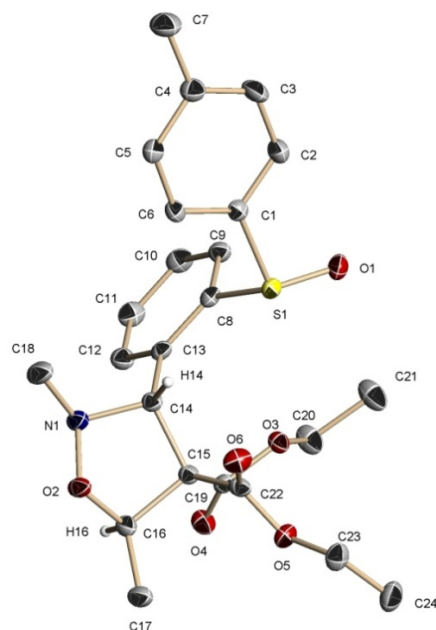

Figure 2

We then studied the reactions of diethyl ethylidene malonate with nitrones **3-5** to check the influence of the substituent at nitrogen on the course of these cycloadditions. Compound **5** remained unaltered after 3 days at 50 ºC in toluene, indicating that the steric hindrance exerted by the *t*-butyl group preclude the approach of the dipolarophile. The easily hydrolysable *N*-benzylnitrone **3** afforded a low amount of the possible adducts, which could not be isolated after 3 days in similar conditions (Scheme 6), whereas *N*-phenylnitrone **4** provided the best result. After 3 days at 50 ºC, starting nitrone had been consumed and isoxazolidine **9a** was obtained with 90% de, and pure diasteromer was isolated in 73% yield (Scheme 6).
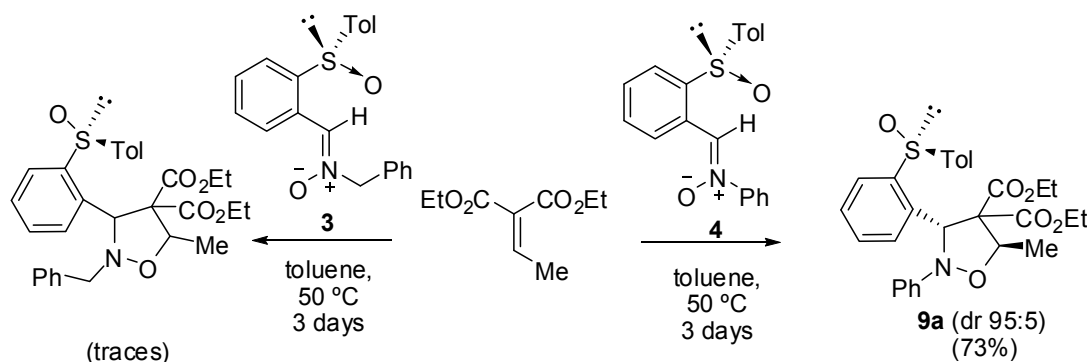
Scheme 6

The last dipolarophile we have studied was the 1,1-bis-phenylsulfonylethylene. After 5 days in toluene at 50 ºC, **2** had disappeared (TLC) and a 60:40 mixture of adducts **10a** and **10b** was isolated in almost quantitative combined yield (Scheme 7). Although the separation of both compounds was not possible in our hands, we could establish by ^{1}H NMR of the mixture, they have the opposite regiochemistry to that observed from diethyl ethylidene malonate. The large size of the two sulfonyl groups must be responsible that the preferred attack of the dipole takes place with the oxygen approaching to the most hindered carbon at dipolarophile, thus minimizing the steric interactions.
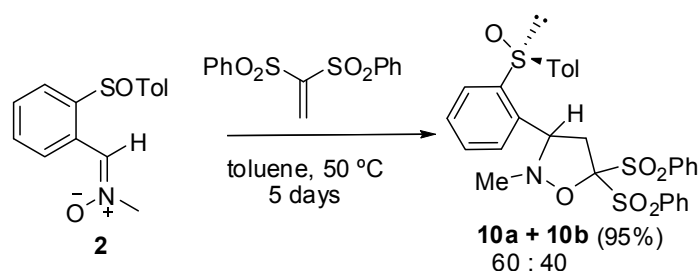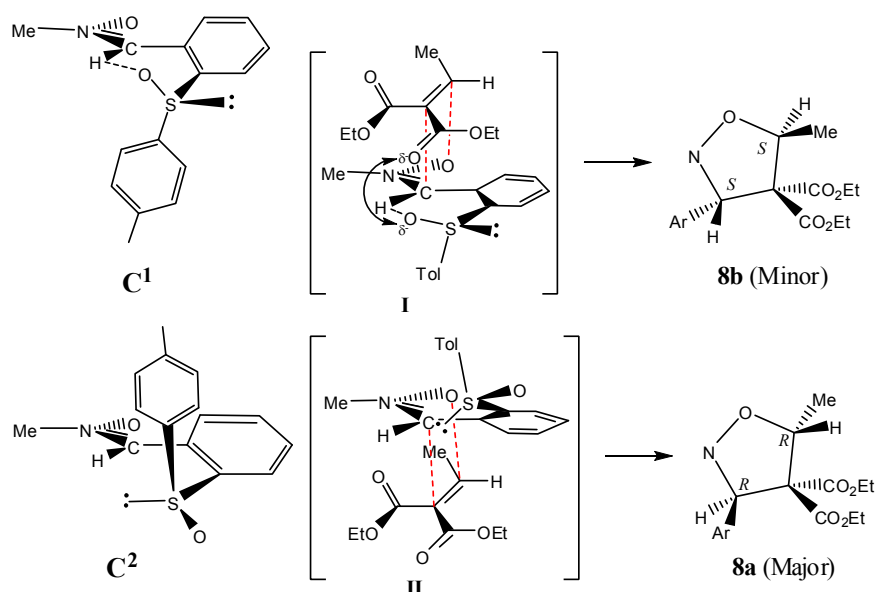

Scheme 7

We have also studied the reactions of **2** with many other gem-disubstituted cyclic and acyclic dipolarophiles, but the results were unsuccessful.

Concerning the course of these reactions, two main questions must be explained. The first one is the reactivity of these nitrones toward dipolarophiles mono or gem-diactivated and the second one the stereoselectivity observed in these processes. We have performed theoretical calculations at the DFT (mPW1PW91)[15] level, with the CPCM model,[16] by using the Gaussian09 program[17] of the relative stability of the different conformations of nitrone **2** at their two possible configurations, *Z* and *E*, around the C=N bond. *Z*-diastereoisomers resulted to be at least 6 kcal/mol more stable than the corresponding *E*-isomers. The two most stable rotamers found in solvent-phase (toluene) for *Z*-**2**, **C**^{1} and **C**^{2}, are indicated in Scheme 8. **C**^{1} is mainly stabilized by the hydrogen bond between the sulfinyl oxygen and the hydrogen at C-1 of the nitrone. **C**^{2} is less stable than **C**^{1} by only 0.6 kcal/mol and arrange the sulfinyl oxygen far from the H at C-1. The orientation of the tolyl group is opposite in both conformations and precludes the approach of the dipolarophile to a different face. It would explain that resulting isoxazolidines exhibit the opposite configuration at the carbon.[18] A similar behavior was observed for *N*-phenylnitrone **4**. Other interesting point is that the most stable conformations predicted by calculations are clearly different to that observed in solid state, because **C**^{1} and **C**^{2} have the aromatic ring conjugated with C=N (coplanar). Finally, we have performed the NBO analyses[18] of the calculated structures that provides information about the charge density localized at the different atoms of the nitrone. From these

calculations a surprising low negative natural charge was assigned to the carbon atom taking part in the double bond at the nitrone (Scheme 8), which could be the related to the reactivity of these dipoles.[20] However, we must also consider that the easy cycloreversion of many of these reactions with strongly stabilized dipolarophiles could be the reason of the apparent low reactivity of these nitrones.

In order to explain the stereochemical course of these reactions, we assume that the approach of the diethyl ethylidenemalonate can only take place to the less hindered face of each of the two most stable conformations of the nitrone ($\mathbf{C^1}$ and $\mathbf{C^2}$). The approach of the dipole to the *Si* face of dipolarophile is favored in order to avoid the interaction of the methyl group at the alkene with the aromatic ring of the nitrone. According to these rules, the two possible TSs will be **I** from $\mathbf{C^1}$ and **II** from $\mathbf{C^2}$ (Scheme 8). The formation of **8a** as the major product suggests the lower stability of the TS **I** which could be explained by the electronic repulsion of the sulfinyl and carbonyl oxygens indicated in Scheme 8. This repulsion would be lower for TS **II** due to the longer distance between both oxygen atoms.

Scheme 8

One interesting transformation we performed on the adducts **8a** and **9a**, resulting in reaction of nitrones with diethyl ethylidene malonate, was observed in the reaction with *t*-BuLi. It initially affords *t*-butyl *p*-tolyl sulfoxide and the corresponding aromatic carbanion, which evolved attacking to the ester group (instead of suffering protonation[20]) and affording the 3,3a,4,8b-tetrahydro-1*H*-indeno[1,2-*c*]isoxazoles **11** and **12** with isolated yields of 58% and 52% respectively (Scheme 9). The transformation involves desimetrization of C-4 of isoxazolidine with generation of a quaternary carbon in a completely stereocontrolled manner. The stereochemistry of the obtained compounds is that resulting in the attack to

the ester group in *cis* arrangement with respect to the phenyl ring where the carbanion is generated (Scheme 9).
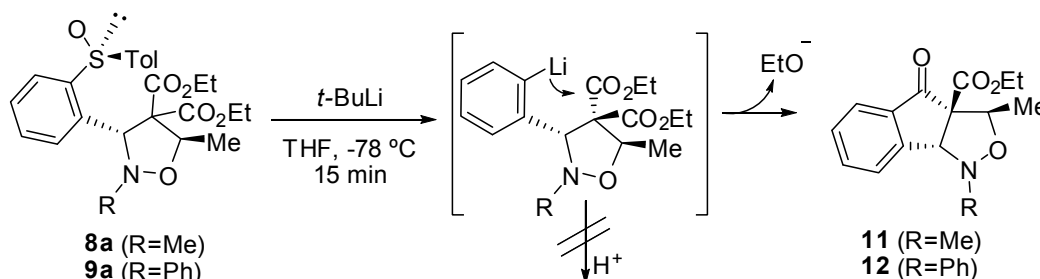
Scheme 9

In conclusion we described the preparation of enantiomerically pure α-2-(*p*-tolylsulfinyl)phenylnitrones and their use as dipoles in asymmetric synthesis. The reactivity of these compounds is dependent on the dipolarophile, the diethyl ethylidenemalonate is reactive and give the best diastereofacial selectivity of 95:5. The major diastereomeric cycloadducts can be transformed into enantiopure tetrahydroindeno[1,2-*c*]isoxazole derivatives on treatment with *t*-butyllithium. Theoretical calculation at DTF level revealed the higher stability of the Z configuration of the nitrones and the existence of two conformations of similar stability the evolution of which allows explaining the observed stereoselectivity.

EXPERIMENTAL

All melting points were determined in open capillary tubes and are uncorrected. IR spectra were determined as it is indicated in each compound with a Bruker FTIR-Vector 22 spectrophotometer. The NMR spectra were determined using TMS as an internal reference on a Bruker AC-300 FT NMR spectrometer operating at 300 and 75 MHz for ^{1}H and ^{13}C NMR, respectively. High resolution mass spectrometry (HRMS), FAB: Waters, VG AutoSpec.The optical rotations were measured at room temperature in the solvent and concentration (gr/100 mL) indicated in each case. Silica gel 60 (230-400 mesh ASTM) and DC-Alufolien 60 F254 were used for flash column chromatography and analytical TLC, respectively. Acetonitrile was dried over activated molecular sieves 4 Å. Microanalyses were carried out on a LECO CHNS-932 in Laboratory of elemental analyses of SIDI of Universidad Autónoma de Madrid, and were in good agreement with the calculated values.

Starting Materials. (*S*)-1-(Diethoxymethyl)-2-(*p*-tolylsulfinyl)benzene[12] was prepared by previously reported procedure. All other chemicals used in this study were commercially available. Geometries were fully optimized in the solvent-phase (toluene with CPCM model) at the DFT (mPW1PW91) level using the

standard 6-31G(d) basis set for all the atoms. Frequencies and zero-point energy (ZPE) were also computed at the same level of theory. Final energies and NBO analysis were obtained using the more extended 6-311G(d,p) basis set for all atoms. Relative free energies (in kcal/mol) were evaluated at the mPW1PW91/6-311G(d,p) level with ZPE and entropy corrections evaluated at 298 K using the frequencies previously calculated at mPW1PW91/6-31G(d) level.

Synthesis of α-(p-tolylsulfinyl)phenylnitrones. **(S)-2-(*p*-Tolylsulfinyl)benzaldehyde (1).** To a solution of (*S*)-1-(diethoxymethyl)-2-(*p*-tolylsulfinyl)benzene (1.27 g, 4.0 mmol) in a mixture of acetone (100 mL) and water (7 mL) was added 0.70 g (2.78 mmol) of pyridinium *p*-toluenesulfonate (PPTS). Then, the mixture was stirred at 50 ºC for 3 h and the solvent was removed under reduced pressure. The residue was dissolved in a mixture of CH_2Cl_2 (100 mL) and water (25 mL). The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (2 x 25 mL). The combined of organic layer was dried (Na_2SO_4) and the solvent removed, the compound **1** was obtained in 98% and used in the next step without any purification; a yellow solid; mp 106-108 ºC; $[\alpha]^{20}_D$ -238.8 (c 1.0, $CHCl_3$); IR (KBr) 1678, 1210, 1022 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.32 (s, 3H), 7.57 and 7.16 (AA'BB' system, 4H), 7.69 (dt, *J* =1.1, 7.4 Hz, 1H), 7.96-7.83 (m, 2H), 8.51 (d, *J* =7.2 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 124.6, 126.6 (2C), 129.7 (2C), 130.6, 132.7, 134.2, 134.9, 141.6, 142.6, 148.1, 190.6; HRMS-(FAB +) *m/z* [M+H⁺] calcd for $C_{14}H_{13}O_2S$: 245.0636, found: 245.0629.

(S,Z)-*N*-Methyl-α-[2-(*p*-tolylsulfinyl)phenyl]nitrone (2). A mixture of aldehyde **1** (2.0 g, 8.2 mmol), *N*-methylhydroxylamine hydrochloride (0.68 g, 8.2 mmol), $NaHCO_3$ (1.4 g, 16.4 mmol), and molecular sieves 4 Å (8.0 g) in 80 mL of absolute EtOH was stirred for 4 days at rt. Then, the reaction mixture was filtered through Celite and washed with EtOH. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (95:5 AcOEt-MeOH) to give **2** (86%); a white solid; mp 115-117 ºC; $[\alpha]^{20}_D$ -210.9 (c 1.0, $CHCl_3$); IR (KBr) 1585, 1436, 1411, 1174, 762, 623 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.82 (s, 3H), 7.24 and 7.39 (AA'BB' system, 4H), 7.55 (m, 2H), 7.90 (m, 1H), 8.11 (s, 1H), 9.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 55.1, 124.9 (2C), 126.5, 128.9, 129.1, 130.1 (2C), 130.5, 131.7, 141.2, 141.6, 141.9; HRMS-ESI *m/z* [M+H⁺] calcd for $C_{15}H_{16}NO_2S$: 274.0902, found: 274.0903. HPLC Daicel Chiralpack AD (75:25 hexane-*i*-PrOH, 1mL/min), 96% *ee*, t_R = 16.8 min. (±)-**2** t_R = 16.4 min and 18.7 min.

(±)-(Z)-N-Benzyl-α-[2-(*p*-tolylsulfinyl)phenyl]nitrone (3). A mixture of racemic aldehyde **1** (244 mg, 1.0 mmol), *N*-benzylhydroxylamine hydrochloride (160 mg, 1.0 mmol), $NaHCO_3$ (168 mg, 2.0 mmol), $MgSO_4$ (481 mg) and of absolute EtOH (10 mL) was stirred for 24 h at rt. Then, the reaction mixture was filtered through Celite and washed with CH_2Cl_2. The filtrate was concentrated under reduced to afford a white solid

in 95% yield. ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.35 (s, 3H), 5.00 (s, 2H), 7.17 (AA'BB' system, 4H), 7.43-7.34 (m, 5H), 7.54 (m, 2H), 7.94 (m, 1H), 8.07 (s, 1H), 9.23 (m, 1H).

(S,Z)-*N*-Phenyl-α-[2-(*p*-tolylsulfinyl)phenyl]nitrone (4). A mixture of 2-(*p*-tolylsulfinyl)benzaldehyde (**1**) (500 mg, 2.05 mmol), *N*-phenylhydroxylamine (374 mg, 3.4 mmol), NaHCO$_3$ (571 mg, 6.8 mmol), 4 g molecular sieves 4 Å and dry CH$_2$Cl$_2$ (20 mL) was heated at 50 °C with vigorous stirring under argon atmosphere for 24 h. After cooling to rt, the reaction mixture was filtered through Celite and the solid was washed with abundant CH$_2$Cl$_2$ and the solvent of filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (3:1 hexane-AcOEt) to give sulfinylnitrone **4** (65%); a yellow oil; $[\alpha]^{20}_D$ -133.7 (c 1.0, CHCl$_3$); ^{1}H NMR (300 MHz, CDCl$_3$) δ 2.34 (s, 3H), 7.21 and 7.38 (AA'BB' system, 4H), 7.47 (m, 3H), 7.57-7.66 (m, 4H), 7.98 (m, 1H), 8.68 (s, 1H), 9.43 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 21.3, 121.6, 125.1, 126.9, 128.4, 129.1, 129.2 (2C), 130.1, 130.3, 130.7, 131.8, 141.4, 141.6, 142.5, 149.1; HRMS-(FAB +) *m/z* [M+H^{+}] C$_{20}$H$_{18}$NO$_2$S: 336.1058, found: 336.1058.

(±)-(Z)-α-[2-(*p*-Tolylsulfinyl)phenyl]-N-*tert*-butylnitrone (5). A mixture of racemic 2-(*p*-tolylsulfinyl)benzaldehyde (**1**) (100 mg, 0.41 mmol), *N-tert*-butylhydroxylamine (88 mg, 0.70 mmol), NaHCO$_3$ (117 mg, 1.4 mmol), 500 mg of molecular sieves 4Å and 5 mL of dry CH$_2$Cl$_2$ was heated at 50 °C with vigorous stirring under argon atmosphere for 3 days. After cooling to rt, the reaction mixture was filtered through Celite and the solid was washed with abundant CH$_2$Cl$_2$ and the solvent of filtrate was removed under reduced pressure. The residue was purified by column chromatography on silica gel (1:1:1 hexane- CH$_2$Cl$_2$-Et$_2$O) to give sulfinylnitrone **5** (10%); and 50 mg of starting aldehyde **1**.^{1}H NMR (300 MHz, CDCl$_3$) δ 1.49 (s, 9H), 2.34 (s, 3H), 7.22 and 7.37 (AA'BB' system, 4H), 7.54 (m, 2H), 7.93 (m, 1H), 8.26 (s, 1H), 9.26 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 21.3, 28.1, 72.0, 124.1, 125.2, 126.8, 129.1, 129.7, 129.88, 129.95, 131.7, 141.5, 141.6, 141.9.

General procedure for cycloaddition reactions. To a stirred mixture of nitrone **2**, **3**, **4** or **5** (0.17 mmol) and dipolarophile (excess), and in any case 0.5 mL of dry toluene, was heated to 50 °C. The reaction was monitored by TLC; after the time indicated in each case, the solvent and/or excess of dipolarophile was removed under reduced pressure and the residue analyzed by ^{1}H NMR and purified by column chromatography on silica gel.

4-Acetyl-2,5-dimethyl-3-[2-(p-tolylsulfinyl)phenyl]isoxazolidines (6a,b): They were obtained as mixture of stereoisomers (**a/b**= *ca.* 1:1) by reaction of nitrone **2** (50 mg, 0.18 mmol) and but-3-en-2-one (0.25 mL), at 50 °C for 4 d without solvent. They were isolated diastereoisomerically pure by column chromatography on silica gel (3:2 hexane-AcOEt).

6a (or b) Rf = 0.33 3:2 (hexane-AcOEt), in 41% yield; colorless oil; $[\alpha]^{20}_{D}$ + 83.5 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.26 (s, 3H), 1.27 (d, J =6.4 Hz, 3H), 2.10 (s, 3H), 2.38 (s, 3H), 3.21 (dd, J =10.0, 7.3 Hz, 1H), 4.34 (d, J =10.0 Hz, 1H), 4.68 (m, 1H), 7.29 (d, J =8.1 Hz, 2H), 7.54-7.44 (m, 5H), 7.97 (m, 1H); ¹³C NMR (CDCl₃) δ 18.6, 21.3, 30.9, 42.0,. 66.9, 69.6, 75.1, 125.7, 126.9, 128.8, 130.0, 130.8, 131.9, 135.5, 141.5, 141.7, 143.3, 206.4; HRMS-(ESI +) m/z [M+H⁺] calcd for C₂₀H₂₄NO₃S: 358.1477, found: 358.1479.

6b (or a) Rf = 0.17 (3:2 hexane-AcOEt); 39% yield; colorless oil; $[\alpha]^{20}_{D}$ -230.7 (c 1.5, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 1.31 (d, J 6.1, 3H), 1.58 (s, 3H), 2.21 (s, 3H), 2.39 (s, 3H), 3.45 (dd, J =10.0, 7.3 Hz, 1H), 4.34 (d, J =10.0 Hz, 1H), 4.71 (m, J =6.4 Hz, 1H), 7.29 (d, J =8.1 Hz, 2H), 7. 45-7.54 (m, 5H), 7.87 (m, 1H); ¹³C NMR (CDCl₃) δ 18.7, 21.4, 31.4, 42.3, 67.0, 69.9, 75.1, 125.3, 126.5, 129.3, 129.5, 130.2, 131.8, 134.5, 140.8, 142.6, 143.3, 205.8; HRMS-(ESI +) m/z [M+H⁺] calcd for C₂₀H₂₄NO₃S: 358.1477, found: 358.1473.

2-Methyl-4-nitro-5-phenyl-3-[2-(p-tolylsulfinyl)phenyl]isoxazolidines (7). They were obtained as mixture of stereoisomers (**a/b**= $ca.$ 1:1) by reaction of nitrone **2** (50 mg, 0.18 mmol) and β-nitrostirene (0.73 mmol) in toluene (0.5 mL) at 50 ºC for 4 d. They were isolated and purified by column chromatography on silica gel (2:1 hexane-AcOEt) in 85% combined yield, but their separation was not possible in our hands; ¹H NMR (300 MHz, CDCl₃) δ 2.27 (s, 3H), 2.33 (s, 3H), 2.42 (s, 3H), 2.55 (s, 3H), 4.40 (dd, J =7.7, 4.8 Hz, 1H), 4.61 (d, J =7.7 Hz, 1H), 4.77 (d, J =7.6 Hz, 1H), 5.05 (dd, J =7.7, 5.1 Hz, 1H), 5.77 (d, J =4.8 Hz, 1H), 5.80 (d, J =5.1 Hz, 1H), 7.12 (d, J =8.0 Hz, 2H), 7.21 (d, J =8.0 Hz, 2H), 7.29-7.63 (m, 20H), 7.83 (m, 1H), 7.88 (m, 1H); ¹³C NMR (CDCl₃) δ 21.2, 21.3, 42.5, 42.6, 70.0, 71.5, 81.8, 82.2, 97.5, 98.1, 125.6, 125.9, 126.4, 126.7, 127.5, 128.1, 128.87, 128.93, 129.07, 129.09, 129.2, 129.7, 129.9, 130.06, 130.12, 131.57, 131.62, 132.2, 132.3, 136.0, 136.3, 140.4, 140.9, 141.7, 141.9, 143.1, 143.5; HRMS-ESI m/z [M+H⁺] calcd for C₂₃H₂₃N₂O₄S: 423.1379, found: 423.1375.

Diethyl 2,5-dimethyl-3-[2-((S)-p-tolylsulfinyl)phenyl]isoxazolidine-4,4-dicarboxylates (8): a mixture of stereoisomers (a/b= 83:17) were obtained from nitrone **2** and 2.5 the equimolecular amount of diethyl ethylidenemalonate after 7 days of reaction at 50 ºC. They were separated by column (3:2 hexane, AcOEt).

(S*S*,3*S*,5*R*)-8a: 75% yield of a white solid, mp 148-150 ºC; $[\alpha]^{20}_{D}$ -148.0 (c 1.0, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 0.80 (t, J =7.2 Hz, 3H), 1.27 (d, J =6.5 Hz, 3H), 1.32 (t, J =7.2 Hz, 3H), 1.97(s, 3H), 2.35 (s, 3H), 3.29 (dq, J =10.7, 7.2 Hz, 1H), 3.76 (dq, J =10.7, 7.2 Hz, 1H), 4.27 (m, 1H), 4.40 (m, 1H), 4.80 (s, 1H), 4.88 (q, J =6.5 Hz, 1H), 7.43 (td, J =7.8, 1.3 Hz, 1H), 7.56 (td, J =7.8, 1.3 Hz, 1H), 7.61 (dd, J =7.8, 1.3 Hz, 1H), 7.24 and 7.68 (AA'BB' system, 4H), 8.22 (dd, J =7.8, 1.3 Hz, 1H); ¹³C NMR (CDCl₃) δ 13.3, 14.1, 14.2, 21.4, 41.9, 61.3, 62.1, 71.9, 72.2, 78.4, 123.3,. 127.7, 128.6, 129.1, 130.0, 130.7, 134.4, 141.8, 142.6,

145.0, 167.3, 168.5. Anal. Calcd for $C_{24}H_{29}NO_6S$; C, 62.73; H, 6.36; N, 3.05; S, 6.98. Found: C, 62.87; H, 6.31; N, 3.13; S, 6.89. HPLC Daicel Chiralpack AD (95: 5 hexane-i-PrOH, 1mL/min), 96% ee, t_R = 36.4 min, ($\pm$)-**8** t_R = 33.0 min and 36.7 min.

(**S***S*,**3***R*,**5***S*)-**8b** colorless oil, 10% yield; [^1]H NMR (300 MHz, CDCl$_3$) δ 0.40 (t, J =6.9 Hz, 3H), 1.21 (t, J= 7.1 Hz, 3H), 1.28 (d, J =6.1 Hz, 3H), 2.32 (s, 3H), 2.67 (s, 3H), 3.23 (m, 1H), 3.54 (m, 1H), 4.17 (m, 2H), 4.98 (q, J =6.1 Hz, 1H), 5.34 (br.s, 1H), 7.18 (m, 2H), 7.33-7. 57 (m, 5H), 7.85 (m, 1H);[^13]C NMR (CDCl$_3$) δ 13.1, 14.1, 14.5, 21.3, 42.8, 60.9, 61.9, 72.3, 72.5, 78.9, 125.6, 125.9, 128.9, 129.5, 129.7, 131.1, 136.5, 141.2, 141.7, 146.0, 167.5, 168.3; HRMS-(ESI +) m/z [M+H[^+]] calcd for $C_{24}H_{30}NO_6S$: 460.1794, found: 460.1786.

(**S***S*,**3***S*,**5***R*) Diethyl 5-methyl-2-pheny-3-[2-p-tolylsulfinyl)phenyl]isoxazolidine-4,4-dicarboxylate (**9a**): it was obtained from nitrone **4** and 2.5 equimolecular amount of diethyl ethilydenemalonate after 24 h, as a colorless oil, in 73% yield after column chromatography on silica gel (2:1 hexane-AcOEt); $[\alpha]^{20}_D$ +5.2 (c 0.5, CHCl$_3$); [^1]H NMR (300 MHz, CDCl$_3$) δ 0.95 (t, J =7.1 Hz, 3H), 1.34 (t, J =7.2 Hz, 3H), 1.41 (d, J =6.4 Hz, 3H), 2.32 (s, 3H), 3.37 (dq, J =10.7, 7.1 Hz, 1H), 3.84 (dq, J =10.7, 7.2 Hz, 1H), 4.25-4.48 (m, 2H), 5.09 (q, J =6.4 Hz, 1H), 5.58 (s, 1H), 6.41 (m, 2H), 6.76-6.83 (m, 3H), 7.05 (d, J =8.0 Hz, 2H), 7.41-7.48 (m, 3H), 7.56 (m, 1H), 7.85 (d, J =7.2 Hz, 1H), 8.20 (dd, J =7.8, 1.0 Hz, 1H); [^13]C NMR (CDCl$_3$) δ 13.4, 14.2 (2C), 21.5, 61.8, 62.3, 70.2, 72.2, 78.1, 117.8, 123.1, 123.2, 127.0, 128.3, 128.8, 129.5, 130.9, 134.9, 140.5, 142.2, 145.1, 148.1, 166.9, 168.2; HRMS-(ESI +) m/z [M+H[^+]] calcd for $C_{29}H_{32}NO_6S$: 522.1950, found: 522.1941.

5,5-Bis(phenylsulfonyl)-2-methyl-3-[2-(p-tolylsulfinyl)phenyl]isoxazolidines (10). A mixture of stereoisomers (**a/b**= 1.5:1) was obtained in 95% yield, after purification by column chromatography on silica gel (1:1 hexane, AcOEt), from nitrone **2** and 1.5 the equimolecular amount of diethyl ethylidenemalonate after 5 days at 50 ºC. [^1]H NMR (300 MHz, CDCl$_3$) δ: 2.21 (s, 3H, **a** isomer), 2.39 (s, 3H, **a** isomer), 2.40 (s, 3H, **b** isomer), 2.57 (s, 3H, **b** isomer), 3.04-2.70 (m, 2H, **a** isomer + 1H, **b** isomer), 3.40 (dd, J =14.8, 6.5 Hz, 1H, **b** isomer), 4.39 (2 dd, 2H, **a** and **b** isomers), 6.84 (d, J =7.6 Hz, 1H, **b** isomer), 7.01 (d, J =7.1 Hz, 1H, **a** isomer).

Tándem desulfinylation-cyclization reaction. To a stirred 0.03 M solution of cycloadducts **8a** or **9a** in dry THF, at -78 ºC and under argon atmosphere, was added 1.7 M t-BuLi in pentane (two equimolecular amount). After stirring for 15 min at -78 ºC, the reaction mixture was quenched with saturated aqueous NH$_4$Cl and extracted with AcOEt. The organic layers were dried over MgSO$_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3:1 hexane-AcOEt).

(3*R*,3a*R*,8b*R*) **Ethyl** **1,3-dimethyl-4-oxo-3,3a,4,8b-tetrahydro-1*H*-indene[1,2-*c*]isoxazolo-3a-carboxylate [(+)-11]**; was obtained from cycloadduct **8a** as colorless oil in 58% yield; $[\alpha]^{20}_D$ +44.5 (c 0.4, CHCl₃); ¹H NMR (500 MHz 50 ºC, CDCl₃) δ 1.30 (t, *J* =7.2 Hz, 3H), 1.47 (d, *J* =6.5 Hz, 3H), 2.90 (s, 3H), 4.24 (m, 2H), 4.39 (q, *J* =6.5 Hz, 1H), 4.88 (brs, 1H), 7.48-7.52 (m, 2H), 7.66 (td, *J* =7.5, 1.1 Hz, 1H), 7.78 (dd, *J* =7.7, 0.6 Hz, 1H); ¹³C NMR (500 MHz, 50 ºC, CDCl₃) δ 14.1, 62.1, 78.3, 125.1, 129.9, 135.6, 166.9, 198.8; HRMS-(ESI +) *m/z* [M+H⁺] calcd for $C_{15}H_{18}NO_4$ (M+H), 276.1230, found: 276.1229 (100%).

(3*R*,3a*R*,8b*R*) **Ethyl** **3-methyl-4-oxo-1-phenyl-3,3a,4,8b-tetrahydro-1*H*-indene[1,2-*c*]isoxazolo-3a-carboxylate [(-)-12]**; was obtained from cycloadduct **9a** as colorless oil in 52% yield; $[\alpha]^{20}_D$ -296.4 (*c* 0.7, CHCl₃); ¹H NMR **(**300 MHz, CDCl₃) δ 1.28 (t, *J* =7.1 Hz, 3H), 1.44 (d, *J* =6.6 Hz, 3H), 4.24 (m, 2H), 4.78 (q, *J* =6.6 Hz, 1H), 5.92 (s, 1H), 7.03 (m, 1H), 7.19 (m, 2H), 7.32 (m, 2H), 7.39 (d, *J* =7.7 Hz, 1H), 7.48 (m, 1H), 7.59 (td, *J* =7.7, 1.2 Hz, 1H), 7.79 (d, *J* =7.7 Hz, 1H); ¹³C NMR **(**CDCl₃) δ 14.1, 17.4, 62.3, 70.4, 75.7, 81.0, 116.2, 122.8, 124.4, 127.0, 128.9, 129.7, 135.2, 135.9, 149.4, 150.2, 165.7, 197.7; HRMS-(ESI +) *m/z* [M+H⁺] calcd for $C_{20}H_{20}NO_4$ (M+H) 338.1392, found: 338.1395 (54%); calcd for $C_{20}H_{19}NO_4Na$ (M+Na) 360.1212, found: 360.1209 (100%).

REFERENCES AND NOTES

1.   (a) J. J. Tufariello, 'Dipolar Cycloaddition Chemistry, ' Vol 2, ed. by A. Padwa, John Wiley and Sons, New York: 1984; chapter 9, p. 83; (b) P. N. Confalone and E. M. Huie, 'Organic Reactions', Vol. 36, ed. by A. S. Kende, John Wiley and Sons, 1988, charter 1, p. 1; (c) M. Harwood and R. J. Vickers, 'Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products,' ed. by A. Padwa and W. H. Pearson, John Wiley-Interscience, 2003; (d) H. Pellissier, *Tetrahedron,* 2007, **63**, 3235; (e) K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863; (f) M. Frederickson, *Tetrahedron,* 1997, **53**, 403.

2.   For some recent examples: (a) V. Nair and T. D. Suja, *Tetrahedron,* 2007, **63**, 12247; (b) A. J. M. Burrell and I. Coldham, *Current Organic Synthesis,* 2010, **7***,* 312; (c) F. A. Davis, N. Theddu, and R. Edupuganti, *Org. Lett.*, 2010, **12**, 4118.

3.   (a) G. Romeo, D. Iannazzoa, A. Pipernoa, R. Romeoa, A. Corsarob, A. Rescifinab, and U. Chiacchio, *Mini-Reviews in Organic Chemistry,* 2005, **2***,* 59; (b) J. Revuelta, S. Cicchi, A. Goti, and

A. Brandi, *Synthesis,* 2007, 485; (c) H. M. I. Osborn, N. Gemmell, and L. M. Harwood, *J. Chem. Soc., Perkin Trans 1*, 2002, 2419.

4.   (a) M. Kissane and A. R. Maguire, *Chem. Soc. Rev.,* 2010, **39**, 845; (b) H. Tsuge, T. Okano, S. Eguchi, and H. Kimoto, *J. Chem. Soc., Perkin Trans 1,* 1997, 1581; (c) N. Katagiri, N. Watanabe, J. Sakaki, T. Kawai, and C. Kanebo, *Tetrahedron Lett.*, 1990, **31**, 4633.

5.   L. M. Stanley and M. P. Sibi, *Chem. Rev.*, 2008, **108**, 2887.

6.   (a) Z.-Z. Huang, Y.-B. Kang, J. Zhou, M.-C. Ye, and Y. Tang, *Org. Lett.,* 2004, **6**, 1677; (b) D. Chen, Z. Wang, J. Li, Z. Yang, L. Lin, X. Liu, and X. Feng, *Chem. Eur. J.,* 2011, **17**, 5226; (c) S. Barroso, G. Blay, M. C. Muñoz, and J. R. Pedro, *Org. Lett.,* 2011, **13**, 402; (d) T. Hashimoto, M. Omote, T. Kano, and K. Maruoka, *Org. Lett.,* 2007, **9**, 4805; (e) L. Weseliński, E. Słyk, and J. Jurczak, *Tetrahedron Lett.*, 2011, **52**, 381.

7.   J. L. Garcia Ruano, J. Alemán, M. B. Cid, M. A. Fernández-Ibañez, M. C. Maestro, M. R. Martín, and A. M. Martín Castro, in *Organosulfur Chemistry in Asymmetric Synthesis*; ed. by T. Toru and C. Bolm, Wiley-VCH, Weinhein, 2008, p. 111.

8.   (a) S. Murahashi, J. Sun, H. Kurosawa, and Y. Imada, *Heterocycles,* 2000, **52**, 557; (b) V. K. Aggarwal, S. J. Roseblade, J. K. Barrell, and R. Alexander, *Org. Lett.,* 2002, **4**, 1227; (c) V. K. Aggarwal, S. Roseblade, and R. Alexander, *Org. Biomol. Chem.,* 2003, **1**, 684.

9.   (a) A. Nuñez Jr., M. R. Martín, A. Fraile, and J. L. García Ruano, *Chem. Eur. J.*, 2010, **16**, 5443; (b) J. L. García Ruano, A. Fraile, M. R. Martin, G. Gonzalez, C. Fajardo, and A. Martin-Castro, *J. Org. Chem.*, 2011, **76**, 3296 and references cited therein.

10.   Ref. 7, p. 123.

11.   Recent references: (a) J. L. García Ruano, E. Torrente, and A. M. Martin-Castro, *J. Org. Chem.*, 2011, **76**, 3597; (b) J. L. García Ruano, A. Parra, I. Alonso, S. Fustero, C. del Pozo, Y. Arroyo, and A. Sanz-Tejedor, *Chem. Eur. J.,* 2011, **17**, 6142 and references cited therein.

12.   C.-Y. Lai, W.-L. Mak, E. Y. Y. Chan, Y.-K. Sau, Q.-F. Zhang, S. M. F. Lo, I. D. Williams, and W.-H. Leung, *Inor. Chem.,* 2003, **42**, 5863.

13.   The authors have deposited atomic coordinates for nitrone **2** and isoxazolidine **8a** with the Cambridge Crystallographic Data Centre (Deposit Number 831759, and 831760, respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. [fax: +44(0)-1223-366033 or e-mail: deposit@ccdc.cam.ac.uk].

14.   The only report concerning cycloaddition of *C,N*-diphenylnitrone to dimethyl ethylidenemalonate was reported in 1973 (M. Joucla, J. Hamelin, and R. Carrie, *Bull. Soc. Chim. Fr.,* 1973, 3116).

15.   (a) J. P. Perdew, S. H. Chevary, K. A. Vosko, K. A. Jackson, M. R. Pederson, D. J. Singh, and C. Fiolhais, *Phys. Rev. B,* 1992, **46**, 6671; (b) J. P. Perdew, S. H. Chevary, K. A. Vosko, K. A. Jackson,

M. R. Pederson, D. J. Singh, and C. Fiolhais, *Phys. Rev. B,* 1993, **48**, 4978; (c) J. P. Perdew, K. Burke, and Y. Wang, *Phys. Rev. B,* 1996, **54**, 16533; (d) C. Adamo and V. Barone, *J. Chem. Phys.,* 1998, **108**, 664. It is proposed that the mPW1PW91 can account for the likely long-range dispersive interactions as well as hydrogen bonding (see: M. P. Patil and R. B. Sunoj, *Chem. Asian J.*, 2009, **4**, 714 and references therein).

16.   (a) V. Barone and M. Cossi, *J. Phys. Chem. A*, 1998, **102**, 1995; (b) M. Cossi, N. Rega, G. Scalmani, and V. Barone, *J. Comp. Chem.*, 2003, **24**, 669.

17.   Gaussian 09, Revision B.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, T. Keith, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2010. (See experimental section for computational details).

18.   A. E. Reed, L. A. Curtiss, and F. Weinhold, *Chem. Rev.,* 1988, **88**, 899. Natural charges on the carbon and nitrogen taking part in the double bond at the nitrone in *Z*-**2** isomers were -0.02 and 0.12 a.u. respectively, for both conformations $\mathbf{C^1}$ and $\mathbf{C^2}$. In the case of *Z*-**4** these values decreased to -0.01 and 0.10 a.u.

19.   We have also performed the NBO analysis of the nitrone lacking of the sulfinyl group. The charge localized at the C and N atoms (0.01 and 0.11 a.u. respectively) increase with respect to that determined for **2**, which means that the presence of the sulfinyl group could be responsible of the decrease in the charge and could also be related to the observed reactivity. Indeed, the decrease in the charge at carbon could be related with the stabilizing interactions (kcal·mol^{-1}), evaluated by means of a second-order perturbational analysis of the Fock matrix, between a lone pair of the sulfinyl oxygen and the C-H antibonding orbital (3.4 for both *Z*-**2** and *Z*-**4**) in the case of $\mathbf{C^1}$, or between the lone pair of the sulfinyl sulphur and the aromatic ring (3.2 for both *Z*-**2** and *Z*-**4**) and the retrodonation from the aromatic ring to the C$_{nitrone}$-C$_{ipso}$ (3.6 for both *Z*-**2** and *Z*-**4**) in the case of $\mathbf{C^2}$.

20.   (a) Y. Arroyo, A. Meana, M. A. Sanz-Tejedor, I. Alonso, and J. L. Garcia Ruano, *Chem. Eur. J.,*

2010, **16**, 9874; (b) J. L. Garcia-Ruano, C. Schoepping, C. Alvarado, and J. Aleman, *Chem. Eur. J.*, 2010, **16**, 8968; (c) J. L. García Ruano, M. A. Fernandez-Ibañez, J. A. Fernandez-Salas, M. C. Maestro, P. Marquez-Lopez, and M. M. Rodriguez-Fernandez, *J. Org. Chem.*, 2009, **74**, 1200.