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The 1,3-Dipolar Cycloaddition Reactions of C, N-Diphenyl Nitrone with Vinyl Sulfoximines

Dorothy M. Davida, Mehdi Bakavolib, Stephen G. Pynea*, Brian W. Skelton^c and Allan H. White^c

^aDepartment of Chemistry, University of Wollongong, Wollongong, N.S.W. 2522, Australia
^b Department of Chemistry, School of Sciences, Ferdowsi University, Mashad, Iran
^cDepartment of Chemistry, University of Western Australia, Nedlands, W.A. 6009, Australia

Abstract: The reactions of vinyl sulfoximines (1a-e) with C, N-diphenylnitrone (2) are highly regioselective and give only 4-sulfonimidoyl-isoxazolidine cycloadducts. These reactions proceed with modest π -facial diastereoselectivity with respect to the dipolarophile. The stereochemical outcome of these reactions is consistent with attack on the favoured ground state conformation of the vinyl sulfoximine through an 'endo' like transition state.

The 1,3-dipolar cycloaddition reaction of nitrones with alkenes is an important method for preparing isoxazolidines in a regioselective and stereoselective manner.¹ Isoxazolidines have been successfully transformed into alkaloids and other important natural products and bioactive molecules.² While the 1,3-dipolar cycloaddition of nitrones and vinyl sulfones³ and sulfoxides⁴ has been studied we were not aware of a similar study on vinyl sulfoximines.⁵ This is surprising since the use of enantiomerically pure vinyl sulfoximines⁶ as dipolarophiles would allow the opportunity for the asymmetric synthesis of chiral isoxazolidines. In this paper we report our studies on the reactions of racemic vinyl sulfoximines (1a-e) with *C*, *N*-diphenylnitrone (2).

Results and Discussion

Heating a chloroform solution of racemic vinyl sulfoximine (1a) or racemic vinyl sulfoximines (1b)-(1e) with C, N-diphenyl nitrone (2) (1.1-1.2 molar equivalents) at 60 °C or 75-80 °C, respectively, in a sealed tube for 16 h to 14-28 days respectively, gave a mixture of two racemic diastereoisomeric cycloadducts (3) and (4) (Scheme 1, although (3) and (4) are racemic only one enantiomer of (3) and (4) are shown for convenience). The results of this investigation are summarized in the Table 1. The diastereoselectivities of these reactions were measured by ¹H NMR (400 MHz) on the crude reaction products. The products appeared to be formed under irreversible (i.e. kinetically controlled) conditions since the diastereoisomeric product ratios did not vary significantly with time over the course of the reaction. In general, the two diastereoisomeric cycloadducts could not be separated by column chromatography and the yields reported in



Yield^b Diastereoselection Entry Vinyl sulfoximine (1) Time R^1 \mathbb{R}^2 (%) (3):(4)(days) 1 (a) H Tos 12h^a 46 65:35 2 (b) Me Tos 14 55 64:36 3 (c) Ph Tos 28 67 67:33 2.4.6-(Pr¹)₃C₆H₂ 4 75:25 (d) Ph -28 66 5 (e) Ph Me 28 43 47:53

Table 1. Reactions of vinyl sulfoximines (1a)-(1e) with nitrone (2).

^a Reaction temperature 60 °C ^b Combined yield of (3) and (4) after column chromatography.

Table 1 refer to the yield of the mixture of (3) and (4) after purification of the crude product by column chromatography. In each case the diastereomerically pure cycloadducts could be obtained by separation by preparative HPLC on a porasil column. ¹H NMR analysis of the pure adducts (3a) and (4a) from the reaction of vinyl *N*-tosyl sulfoximine (1a) with (2), revealed that these adducts were two diastereoisomeric 4sulfonimidoyl-isoxazolidines rather than the regio-isomeric 5-sulfonimidoyl-isoxazolidines (5a). This is in contrast to the reaction of phenyl vinyl sulfone³ and *p*-tolyl vinyl sulfoxide⁴ with nitrones. The reaction of the former alkene with *C*-phenyl-*N*-methylnitrone was not regioselective and gave a mixture of 4-phenylsulfonyland 5-phenylsulfonyl-isoxazolidines (68 : 32, respectively).³ The reaction of the latter alkene with (2) however, was completely regioselective and gave in 54% and 3% isolated yields two diastereoisomeric 4-*p*tolylsulfinylisoxazolidines.⁴

The reaction of *N*-tosyl (*E*)-propenyl sulfoximine (**1b**) and (**2**) proceeded with a similar diastereoselectivity as the reaction of (**1a**) and (**2**) and gave a 64 : 36 mixture of cycloadducts (**3b**) and (**4b**) respectively (Table 1, entry 2). The regiochemistry of these adducts was evident from analysis of their ¹H and COSY NMR spectra. The relative '*endo*' stereochemistry of (**3b**) and (**4b**), rather than the relative '*exo*' stereochemistry as shown in structure (**6**), was determined from NOESY NMR experiments. The results of these experiments are summarized in the Experimental section of this paper. The high regioselectivity and preference for '*endo*' diastereoselectivity in this reaction is similar to that found in the reaction of the analogous (*E*)-propenyl phenyl sulfone with *C*-phenyl-*N*-methylnitrone which gave 84% isolated yield of the

'endo'-4-phenylsulfonyl-isoxazolidine cycloadduct and 5% isolated yield of the 'exo'-4-phenylsulfonylisoxazolidine cycloadduct.^{3b}

The reaction of N-tosyl β -styryl sulfoximine (1c) with (2) proceeded with similar diastereoselectivity as the other N-tosyl vinyl sulfoximines, (1a) and (1b), and gave a 67 : 33 mixture of the cycloadducts (3c) and (4c) (Table 1, entry 3). The relative stereochemistry of (3c) was unequivocally determined by a single crystal structural analysis, as shown in Fig. 1. The structural analysis showed (3c) had the 'endo' relative stereochemistry and this knowledge was used to assign the relative stereochemistry of the major and minor cycloadducts (3a, b) and (4a, b), respectively.



Figure 1. Molecular projection of (3c) normal to the central ring plane; 20% thermal ellipsoids are shown for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å.

The sterically demanding analogue of (1c), the *N*-2,4,6-triisopropylphenylsulfonyl β -styryl sulfoximine (1d) upon reaction with nitrone (2) gave a 75 : 25 mixture of the cycloadducts (3d) and (4d) respectively. The relative stereochemistry assigned to the cycloadducts (3d) and (4d) was based upon the close similarity of their ¹H NMR spectra to those of (3c) and (4c) respectively.

The reaction of the N-methyl β -styryl sulfoximine (1e) with nitrone (2) was poorly diastereoselective and gave a 53 : 47 mixture of the diastereoisomeric '*endo*' cycloadducts (4e) and (3e) respectively. Thus unlike vinyl sulfones,³ the regioselectivity and diastereoselectivity of the reaction of the N-tosyl vinyl sulfoximines (1a-c) with nitrone (2) was independent upon the nature of the β -vinyl substituent (R¹). The

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diastereoselectivities of the reactions, although only modest, increased as the steric demand of the *N*-substituent (\mathbb{R}^2) of the sulfoximine was increased from methyl through to 2,4,6-triisopropylphenylsulfonyl. The stereochemical outcome of the reaction of (1c) and (2) can be accounted for by invoking the 'endo' transition state (A) in which the least sterically demanding substituent on the sulfoximine, the oxygen substituent, is approximately syn-coplanar with the β -vinyl hydrogen. Addition of the nitrone then occurs from the less hindered β -face of the alkene, that is *anti* to the bulky *S*-phenyl substituent. We have recently found a similar s-cis conformation for (1c) in the solid state to that shown for (1c) in transition state structure (A).⁷



It is well documented that the reaction of nitrones with 1,1-disubstituted alkenes gives 5,5disubstituted isoxazolidines.^{1b} Therefore in an attempt to reverse the regiochemistry of these dipolar cycloadditions we prepared the α -bromo vinyl sulfoximines (7) and (8) (Scheme 2). ¹H NMR analysis of the reaction of (2) and (7) in CDCl₃ solution after 24 h at room temperature revealed 66% conversion to the expected 5,5-disubstituted isoxazolidine cycloadduct (9) which was a 2.6:1 mixture of diastereoisomers. (Major diastereoisomer: ¹H NMR (CDCl₃) δ 5.84 (dd, J= 8.4, 3.9 Hz, 1H, H3), 4.09 (dd, J = 14.4, 3.9 Hz, 1H, H4), 3.65 (dd, J = 14.4, 8.4 Hz, 1H, H4'). Minor diastereoisomer: ¹H NMR (CDCl₃) δ 5.92 (dd, J = 7.8, 5.1 Hz, 1H, H3), 3.96 (dd, J = 14.4, 5.1 Hz, 1H, H4), 3.97 (dd, J= 14.4, 7.8 Hz, 1H, H4'). Similarly, the reaction between (2) and (8) showed 60% conversion to the cycloadduct (10) as a 1.8:1 mixture of diastereoisomers after 24 h at room temperature . (Major diastereoisomer: ¹H NMR (CDCl₃) δ 5.78 (dd, J = 8.8, 4.4 Hz, 1H, H3), 4.09 (dd, J = 14.0, 4.4 Hz, 1H, H4), 3.65 (dd, J = 14.0, 8.8 Hz, 1H, H4'). Minor diastereoisomer: δ 6.03 (dd, J = 3.9, 7.2 Hz, 1H, H3), 3.90 (dd, J = 14.4, 3.9 Hz, 1H, H4), 3.59 (dd, J = 14.4, 7.2 Hz, 1H, H4')). However, after 48 h these cycloadducts were no longer evident and a mixture of unidentified products resulted. We assume that these compounds are thermally unstable due to the sensitive tertiary bromide group. These reactions were therefore not further studied.

Scheme 2



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In summary, the reaction of vinyl sulfoximines (1a-e) with C,N-diphenylnitrone (2) are highly regioselective and only 4-sulfonimidoyl-isoxazolidine cycloadducts are obtained. These reactions proceed with modest π facial diastereoselectivity with respect to the dipolarophile. The stereochemical outcome of these reactions is consistent with attack on the favoured ground state conformation of the vinyl sulfoximine through an 'endo' like transition state.

Experimental

Vinyl sulfoximines (2b), (2c) and (2e) were prepared as previously reported.⁷ All NMR spectra (¹H NMR and ¹³C NMR) were recorded on a Varian unity 400 or 300 NMR spectrometer in CDCl₃ solution unless otherwise indicated. Aromatic protons have been assigned as belonging to the aromatic rings Ar₁-Ar₅ as shown in the structures below. 2-D NMR (COSY and NOESY) was used to confirm the ¹H assignments.



Melting points were measured on a capillary melting point apparatus and are uncorrected. HPLC separations were performed using a Waters Model 510 pump, a Waters 25 x 10 cm Radial-Pak HPLC porasil cartridge with detection at 254 nm.

X-ray Structure Determinations. A unique room temperature (-295K) diffractometer data set (molybdenum Mo K α monochromatic radiation. $\lambda = 0.7109_3$ Å; ($2\phi_{max} = 50^{\circ}. 2\phi/\phi$ scan mode) yielded 5335 independent reflections (gaussian absorption correction), 2043 with $I > 3\sigma(I)$ being considered 'observed' and used in the full matrix least squares refinement. Anisotropic thermal parameters were refined for C, N, O, S; (x, y, z, U_{is0})_H were included constrained at estimated values after observation in difference maps. Conventional residuals *R*. R_w on /*F*/ were 0.063, 0.059 (statistical weights derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + 0.0004 \sigma^4(I_{diff})$). Full tabulations of atom coordinates and thermal parameters, molecular geometries and structure factor amplitudes have been deposited with the Cambridge Crystallographic Data Centre. Crystal data for (3c): $C_{34}H_{30}N_2O_4S_2$. M = 594.8 Monoclinic, space group $P_{24,e}(C_{2h}^{\circ}$. No. 14), a = 10.398 (2), b = 111.885(6), c = 26.036(5) Å, $\beta = 109.42(2)^{\circ}$, V = 3034(2) A³. $D_c(Z) = 4^{\circ} = 1.30$ g, cm ⁻³; F(000) = 1248. $\mu_{M0} = 2.2$ cm.⁻¹; specimen; 0.23 x 0.42 x 0.09 mm; $A *_{min,max} = 1.02^{\circ}$.

N-Tosyl *S*-ethenyl *S*-phenyl sulfoximine (1a). *N*-Tosyl *S*-methyl *S*-phenyl sulfoximine⁸ (4.0 g, 13 mmol) was dissolved in freshly distilled dry THF (55 mL) under N₂ and then cooled to -78 °C. Butyllithium / hexanes -16 mmol) was added slowly at this temperature then the reaction was allowed to warm up to rt over 35 min. The reaction was recooled to -78 °C and Eschenmoser's salt (4.8g, 26 mmol) was added under N₂ and the reaction stirred at -78 °C for 1 h. The mixture was then allowed to come to room temperature then rotary evaporated to remove solvent. The residue was dissolved in methanol (40 mL) then iodomethane (12 mL, 190 mmol) was added and the mixture was left stirring overnight. The reaction was placed in a 40 °C water bath for 2 h to remove excess iodomethane before being rotary evaporated to remove solvent. The erude product was then shaken with a 5% aqueous solution of sodium bicarbonate (280 mL) and CH₂Cl₂ (200 mL) until all the oil and solid had dissolved. The CH₂Cl₂ layer was separated and the aqueous layer washed with a further 150 mL of CH₂Cl₂. The organic extracts were combined, washed with a 10% aqueous solution

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of sodium thiosulfate (100 mL) then with a saturated aqueous solution of NaCl (200 mL), dried over MgSO₄ and rotary evaporated to dryness. The orange oil was chromatographed on silica gel using 50% ethyl acetate / hexane as eluent to give 1.1 g (26 %) of (1a) as a white solid, m.p 126-128 °C. ¹H NMR (CDCl₃) δ 7.97 (dd, J = 7.8, 0.9 Hz, 2H, Ar₄ 'ortho'), 7.85 (dd, J = 8.1, 1.8 Hz, 2H, Ar₁ 'ortho'), 7.68 (t, J = 7.8 Hz, 1H, Ar₄ 'para'), 7.57 (t, J = 7.8 Hz, 2H, Ar₄ 'meta'), 7.26 (d, J = 8.1 Hz, 2H, Ar₁ 'meta'), 6.83 (dd, J = 16.2, 9.6 Hz, 1H, <u>H</u>1), 6.48 (dd, J = 16.2, 1.5 Hz, <u>H</u>2'), 6.19 (dd, J = 9.6, 1.5 Hz, <u>H</u>2), 2.40 (s, 3H ArC<u>H</u>₃). ¹³C NMR (CDCl₃) δ 161.77 (C), 142.85 (C), 137.73, 134.23, 129.64, 129.24, 129.14 (CH₂), 128.04, 126.68, 102.37(C), 21.49 (<u>C</u>H₃). HRMS (El) calcd for C ₁₅ H₁₅NO₃S₂ 321.04931 found 321.05039.

N-Tosyl *S*-(1-bromo-1-ethenyl) *S*-phenylsulfoximine (7). To a solution of (1a) (0.521 g, 1.6 mmol) in CCl₄ / CH₂Cl₂ (1:1, 12 mL) was added Br₂ (3.2 mmol) in CCl₄ solution (5 mL) and the reaction stirred over night under N₂ in a flask that was covered in aluminium foil to exclude light. After 24 h an aqueous 10% solution of sodium thiosulfate was added until the bromine colour disappeared and then CH₂Cl₂ (20 mL) was added. The organic layer was separated, dried (MgSO₄) then rotary evaporated to remove solvent. The residue was redissolved in CH₂Cl₂ (15 mL) and treated with triethylamine (0.181g, 1.78 mmol) for 40 min. The solution was washed with 5% aqueous HCl and then water. The solution was then dried (MgSO₄) and evaporated to dryness. Purification by column chromatography using 40% EtOAc / hexane as eluent gave pure (7) (0.223 g . 32%) as an oil. ¹H NMR δ 8.01 (dd, J = 6.0, 4.2 Hz, 2H, Ar₄ 'ortho'), 7.89 (dd, J = 6.6, 1.8 Hz, 2H, Ar₁ 'ortho'), 7.71 (t, 1H, Ar₄ 'para'), 7.58 (t, 2H, Ar₄ meta'), 7.30 (d, J = 3.6 Hz, 1H, H1), 6.47 (d, J = 3.9 Hz, 1H, H1'), 2.340 (s, 3H, ArCH₃). ¹³C NMR δ 143.10 (C), 140.42 (C), 134.81, 134.44, 131.43 (CH₂), 129.39, 129.26, 129.11, 128.69 (C), 126.75, 21.49 (CH₃). Mass spectrum (ES+) *m/z* 402/400 (84%/100%, [M]⁺), 294 (25) 283 (65). HRMS (EI) caled for C₁₅H₁₄Br⁷⁹NO₃S₂ 398.95991, found 398.95910:

N-2.4.6-(Triisopropylbenzenesulfonyl) *S*-methyl *S*-phenylsulfoximine. To a solution of *S*-methyl *S*-phenyl sulfoximine⁸ (7.6 g, 49 mmol) of in dry CH₂Cl₂ (20 mL) was added dry pyridine (6 mL) and a crystal of dimethylaminopyridine. The mixture was cooled to 0 °C then 2,4,6-triisopropylbenzenesulfonyl chloride (14.85 g, 49 mmol) was added in small lots under a flow of N₂. After addition the mixture was warmed to rt and was stirred under N₂ for 16 h. The reaction was filtered, the solids washed with dry pyridine (10 mL) and the filtrate was diluted with water (50 mL) and extracted three times with CH₂Cl₂. The combined extracts were washed with 10% aqueous HCl (2 x 25 mL) then dried over MgSO₄, filtered and rotary evaporated to dryness. The residue was recrystallized from ethanol to give 11 g (53%) of the title compound as white crystals mp 138-139 °C. ⁻¹H NMR δ 7.99 (cd, J = 8.4, 15 Hz, 2H, ArH), 7.69 (ut, 1H, ArH), 7.58 (ut, 2H, ArH). 7.11 (s, 2H, Ar₁ meta⁵), 4.38 (hept, 2H, Me₂CH), 3.11 (s, 3H, CH₃), 2.88 (hept, 1H, Me₂CH), 1.255 1.251 1.233 1.230 1.207 (3 x d, overlapping, 6CH₃). ⁻¹³C NMR δ 151.95, 149.05, 138.99, 137.26, 134.18, 129.59, 127.42, 123.37, 46.95, 34.12, 29.25, 24.65 (2CH₃), 24.60 (2CH₃), 23.63 (CH₃), 23.61 (CH₃). Mass spectrum (ES+) *m/z* 422/400 (100%, [M+H]⁺).

N-(2,4,6-Triisopropylbenzenesulfonyl) *S*-ethenyl *S*-phenylsulfoximine (1f) The title compound was prepared from *N*-2,4,6-(triisopropylbenzenesulfonyl) *S*-methyl *S*-phenylsulfoximine (4.44 g, 11.0 mmol) using the procedure described above for the synthesis of (1a). Recrystallisation from ethanol gave 1.94g (42%) of white crystals, m.p. 155-156 °C. ¹H NMR δ 7.96 (dd, J = 8.1, 1.5 Hz, 2H, Ar₄ 'ortho'), 7.66 (t, J = 7.5 Hz, 1H, Ar₄ para). 7.59 (t, J = 8.1 Hz, 2H, Ar₄ 'meta'), 7.12 (s, 2H, Ar₁ 'meta'), 6.82 (dd, J = 16.5, 9.6 Hz, 1H, <u>H</u>1), 6.48 (dd, J = 1.2, 16.2 Hz, 1H, <u>H</u>2'), 6.16 (dd, J = 9.6, 1.2 Hz, 1H, <u>H</u>2), 4.38 (quin, 2H, Me₂C<u>H</u>), 2.88 (quin, 1H, Me₂C<u>H</u>), 1.25 (d, J = 1.8 Hz, 6H, 2C<u>H</u>3), 1.23 (d, J = 1.2 Hz, 12H, 4C<u>H</u>3). ¹³C NMR δ 151.99, 149.11,

138.09, 134.10, 129.55, 128.76, 127.98, 127.41, 123.35, 34.11 (CH), 29.24 (CH), 24.66 (<u>CH</u>₃), 24.58 (<u>CH</u>₃), 23.63 (<u>C</u>H₃). HRMS (EI) calcd for C₂₃H₃₁NO₃S₂ 433.1745 found 433.17359.

N-(2,4,6-Triisopropylbenzenesulfonyl) *S*-(1-bromo-1-ethenyl) *S*-phenylsulfoximine (8). To a stirred solution of (1f) (0.518 g 1.01 mmol) in CH₂Cl₂ (5 mL) was added Br₂ (0.21 g, 1.3 mmol) in dry CCl₄ (3 mL) and the reaction stirred under N₂ for 16 h. TLC showed the reaction was 50% complete so another equivalent of bromine was added and the reaction was left stirring for a further 24h. The reaction mixture was worked up as described above for the preparation of (7). The residue was then treated with tricthylamine (0.149g, 1.47 mmol) for 2.5 h and then worked up as described above for the synthesis of (7) to give an oil. (0.585 g). ¹H NMR analysis showed a showed a 2:1 mixture of (8) and (1f). Purification by column chromatography using 25% EtOAc / hexane as eluent gave 0.162 g (26%) of (8) as an oil. ¹H NMR δ 8.01 (dd, J = 8.8, 1.2 Hz, 2H, Ar₄ 'ortho'), 7.70 (t, J = 7.6 Hz, 1H, Ar₄ 'para'), 7.57 (t, J = 8.4 Hz, 2H, Ar₄ 'meta'), 7.31 (d, J = 3.6 Hz, 1H, H2), 7.13 (s, 2H, Ar₁ 'meta'), 6.47 (d, J = 3.2 Hz, 1H, H2'), 4.43 (hept, J = 6.8 Hz, 2H, Me₂C<u>H</u>), 2.88 (hept, J = 6.8 Hz, 1H, Me₂C<u>H</u>), 1.27 (d, J = 6.4 Hz, 6H, 2C<u>H₃</u>), 1.24 (d, J = 6.4 Hz, 6H, 2C<u>H₃</u>), 1.22 (d, J = 6.4 Hz, 6H, 2C<u>H₃</u>); ¹³C NMR δ 152.13 (C), 149.15 (C), 137.13 (C), 135.08 (C), 134.65 (CH), 130.92 (CH₂), 129.31 (CH), 128.96 (CH), 123.36 (CH), 34.06 (Me₂CH), 29.23 (2Me₂CH), 24.67 (<u>CH₃</u>), 24.55 (2<u>CH₃</u>), 23.54 (2<u>C</u>H₃). HRMS (+LSIMS) caled for C₂₃H₃₀⁸¹BrNO₃S₂+H 514.090786 found 514.08506.

N-2,4,6-(Triisopropylbenzenesulfonyl) *S*-2-phenylethenyl *S*-phenylsulfoximine (1d). To a stirred solution of *N*-2,4,6-(triisopropylbenzenesulfonyl) *S*-methyl *S*-phenyl sulfoximine (2.1 g, 4.95 mmol) in dry THF (20 mL) under N₂ at -78 °C was added butyllithium in hexanes (5.88 mmol). The reaction mixture was then allowed to come to rt and was stirred for 10 min. The mixture was then recooled to -78 °C and benzaldehyde (0.74g, 7.5 mmol) was added, the reaction was warmed slowly to 0 °C and stirred for 45 min. Dry triethylamine (0.73 mL, 5.5 mmol) was added followed by the dropwise addition of methanesulfonyl chloride (0.629 g, 5.49 mmol). The reaction was stirred for 20 min then triethylamine (0.73 mL) was added and the reaction allowed to come to rt and stirred another 20 min. A 10% aqueous solution of NH₄Cl (10 mL) was added and the mixture was extracted with CH₂Cl₂. The extracts were dried (MgSO₄) and rotary evaporated to dryness to give a solid material. Recrystallization from ethyl acetate gave fine white crystals. (0.447g, 17%), mp 202-206 °C. ¹H NMR δ 8.01 (d, J = 7.6 Hz, 2H, Ar<u>H</u>), 7.67 (d, J = 15.2 Hz, 1H, C<u>H</u>), 7.63 (d, J = 7.6 Hz, 2H, Ar<u>H</u>), 7.45-7.38 (m, 5H, Ar<u>H</u>), 7.11 (m, 2H, Ar₁ 'meta'), 6.88 (d, J = 15.2 Hz, 1H, C<u>H</u>). 4.41 (m, 2H, Me₂C<u>H</u>), 2.87 (m, 1H, Me₂C<u>H</u>), 1.23 (ddd, 18H, 6C<u>H</u>₃). Anal. Caled for C₂9H 35NO₃S₂ : C, 68.34; H, 6.92; N, 2.75. Found C, 68.28; H, 7.03, N, 2.68.

Reaction of Vinyl Sulfoximines (1a) with Nitrone (2)-A General Procedure: The vinyl sulfoximine (1a) (0.203 g, 0.632 mmol) nitrone (2) (0.142 g, 0.758 mmol) and chloroform (3 mL) were placed in a sealed tube, with a stirring bar, under N₂. The tube was covered with foil to exclude light and the solution was heated at 60 °C overnight. The crude ¹H NMR indicated the ratio of diastereoisomers was 65:35. The reaction mixture was purified by column chromatography on silica gel using 40% ethyl acetate in hexane as eluent. Fractions were obtained that contained a mixture of the two diastereoisomers (3a) and (4a) (0.152g, 46%). A small sample of this mixture was separated by HPLC using 15% ethyl acetate / hexane as the mobile phase. The first compound to elute was (3a), the second, (4a).

(3*SR*, 4*SR*, *SSR*) 2.3-Diphenyl-4(*N*-*p*-tolylsulfonyl *S*-phenylsulfonimidoyl)isoxazolidine (3a): Oil; ¹H NMR (C₆D₆) δ 8.18 (d, J = 7.8 Hz, 2H, Ar<u>H</u>), 7.67 (m, 4H, Ar<u>H</u>), 7.15 (m, 3H, Ar<u>H</u>), 6.88-6.61 (m, 10H, Ar<u>H</u>), 5.14 (d, J = 3.9 Hz, 1H, <u>H</u>3), 4.63 (quin, J = 3.9, 7.8, 11.4 Hz, 1H, <u>H</u>4), 4.27 (dd, J = 10.6, 4.5 Hz, 1H, <u>H</u>5), 3.87 (dd, J = 10.5, 7.5 Hz, <u>H</u>5), 1.87 (s, 3H, C<u>H</u>3), ^{1.4}C NMR δ 151.4, 148.6, 142.9, 140.5, 139.07,

134.85, 129.56, 129.41, 129.29, 129.12, 128.67, 128.44, 126.95, 126.63, 122.82, 115.39, 79.26, 69.70, 66.62, 29.69 (CH₃). Mass spectrum (ES+) m/z 519 (81% [M+H]+), 501 (59), 443 (20), 279 (78), 275 (20), 165 (100). HRMS (+LSIM) calcd for C₂₈H₂₆N₂O₄S₂+H, 519.141184 found 519.14010. NOESY cross-peaks were observed between Ar₂ ortho' and H3 and H5.

(3RS, 4RS, SSR) 2,3-Diphenyl-4(*N*-*p*-tolylsulfonyl-*S*-phenylsulfonimidoyl)isoxazolidine (4a) Oil; ¹H NMR (C₆D₆) δ 8.17 (d, J = 8.1 Hz, 2H, Ar<u>H</u>), 7.67 (d, J = 7.2 Hz, 2H, Ar<u>H</u>), 7.16 (m, 3H, Ar<u>H</u>), 6.96 (m, 5H, Ar<u>H</u>), 6.76 (m, 7H, Ar<u>H</u>), 4.77 (d, J = 4.2 Hz, 1H, <u>H</u>3), 4.60 (dd, J = 10.2, 3.6 Hz, 1H, <u>H</u>5), 4.17 (m, 1H, <u>H</u>4), 3.94 (dd, J = 10.2, 7.2 Hz, <u>H</u>5'), 1.89 (s, 3H, C<u>H</u>₃). ¹³C NMR δ 148.41, 142.91, 140.46, 138.06, 135.77, 134.67, 129.67, 129.25, 129.07, 128.93, 128.68, 128.44, 126.98, 126.60, 123.49, 116.46, 78.28, 70.44, 66.15, 29.70. Mass spectrum (ES+) *m/z* 519 (100%, [M+H]+), 541 (17, [M+Na]+), 501 (82).

(3SR, 4SR, 5SR, SSR) 5-Methyl-2,3-diphenyl-4(N-p-tolylsulfonyl S-phenylsulfonimidoyl)isoxazolidine (3b) and (3RS, 4RS, 5RS, SSR) 5-Methyl-2,3-diphenyl-4(N-p-tolylsulfonyl S-phenylsulfonimidoyl) isoxazolidine (4b). The title compounds were obtained from the reaction of the vinyl sulfoximine (1b) (97.5 mg, 0.29 mmol) and the nitrone (65.8 g, 0.33 mmol) in CDCl₃ (1 mL) at 75-80 °C for 14 days using the general procedure described above. ¹H NMR of the crude reaction mixture showed an diastereomeric ratio of 1.75:1. The reaction was chromatographed on silica gel using ethyl acetate / hexane (1 : 2) as eluent to give an almost pure sample of (3b) (12 mg) and a mixed fraction (73 mg) of (3b) and (4b) (total yield 55 %). A small sample of the mixture was separated by HPLC using 15% EtOAc / hexane as the mobile phase, the first compound from the column was (3b) and the second (4b).

(3b): Oil; ¹H NMR δ 7.88 (d, J = 7.6 Hz, 2H, Ar₄ ortho'), 7.77 (d, J = 8.0 Hz, 2H, Ar₄ 'ortho'), 7.59 (t, 1H, Ar₄ 'para'), 7.53 (d, J = 7.6 Hz, 2H, Ar₃ 'ortho'), 7.45 (m, J = 8.0 Hz, 2H, Ar₄ 'meta'), 7.36 (m, 2H, Ar₃, 'meta'), 7.31 (d, 1H, J = 7.2 Hz, Ar₃ 'para'), 7.24 (d, 2H, J = 8.4 Hz, Ar₁ 'meta'), 7.11 (dd, 2H, J = 7.6, 8.4 Hz, Ar₂ 'meta'), 6.89 (t, 1H, Ar₂ 'para'), 6.69 (d, 2H, Ar₂ 'ortho'), 5.25 (d, J = 3.6 Hz, 1H, <u>H</u>3), 4.54 (quin, J = 6.4 Hz, 1H, <u>H</u>5), 4.23 (dd, J = 3.6, 6.4 Hz, 1H, <u>H</u>4), 2.41 (s, 3H, MeAr), 1.29 (d, J = 6.0 Hz, 3H, C<u>H</u>₃), ¹³C NMR δ 149.00, 142.86, 140 62, 139.86, 134.92, 134.86, 129.64, 129.25, 129.16, 129.01, 128.91, 128.05, 126.68, 126.53, 122.09, 114.21, 84.21, 75.23, 70.20, 24 54, 18.55. Mass spectrum (EI+) *m/z* 533 (22%, [M+H]+), 555 (68, [M+Na]+), 570 (10, ·M+K]+, 489 (38), 288.5 (100)). NOESY cross-peaks were observed between, C5Me and H4; Ar₃ ortho and H4; Ar

(4b): Oil: ¹H NMR δ 7.88(d, J = 8.1Hz, 2H, Ar₄ ortho⁵), 7.69 (d, J = 8.4 Hz, 2H, Ar₁ 'ortho⁵), 7.63 (m, 1H, Ar₄ para⁵), 7.48 (t, 2H, Ar₄ ineta.), 7.26-7 10 (m, 9H, Ar₁ ineta., Ar₂ ineta', Ar₃ 'ortho +meta + para'), 6.92 (t, J = 6.9 Hz, 1H, Ar₂ [para), 6.77 (d, J = 8.7 Hz, 2H, Ar₂ 'ortho⁵), 4.92 (d, J = 4.8 Hz, 1H, <u>H</u>3), 4.82 (m, J = 6.3 Hz, 1H, <u>H</u>5), 4.01 (dd, J = 6.3, 4.8 Hz, 1H, <u>H</u>4) 2.40 (s, 3H, MeAr), 1.49 (d, J = 4.5 Hz 3H, C<u>H</u>₃), ¹³C NMR δ 148.98, 142.81, 140.43, 139.27, 136.06, 134.78, 129.73, 129.20, 129.03, 128.92, 128.86, 128.05, 126.57, 126.53, 122.48, 120.46, 114.87, 83.71 (C4), 75.19 (C5), 70.81 (C3), 21.53, 19.24. HRMS (CI) calcd for 533.15683, found 533.15607. NOESY cross-peaks were observed between, H3 and H5; and H3 and H5.

(3SR, 4SR, 5SR, SSR) 2,3,5-Triphenyl-4(*N*-*p*-tolylsulfonyl S-phenylsulfonimidoyl)isoxazolidine (3c) and (3RS, 4RS, 5RS, SSR) 2,3,5-Triphenyl-4(*N*-*p*-tolylsulfonyl S-phenylsulfonimidoyl)isoxazolidine (4c). The title compounds were obtained from the reaction of the vinyl sulfoximine (1c) (0.083 g, 21.1 mmol) and the nitrone (0.42 g, 0.21 mmol) in CHCl₃ (1.5 mL) at 75-80 °C for 28 days using the general procedure described above. ¹H NMR of the crude reaction mixture showed an diastereometric ratio of 2 : 1. The reaction was chromatographed on silica get using ethyl acetae (hexane (1 : 2) as eluent to give 0.085 g (67%) of a mixture

of (3c) and (4c). A sample was separated by HPLC using 10% EtOAc / hexane as the mobile phase to give pure samples of (3c) and (4c) as white solids. A crystal structure was obtained on (3c), Fig. 1.

(3c): ¹H NMR δ 7.78 (d, J = 7.2 Hz, 2H, Ar<u>H</u>), 7.75 (d, J = 8.1 Hz, 2H, Ar<u>H</u>), 7.54 (t, J = 7.8 Hz 1H, Ar<u>H</u>), 7.52 (dd, J = 8.4 Hz, 2H, Ar<u>H</u>), 7.39 (d, J = 8.1 Hz, 2H, Ar<u>H</u>), 7.34 (d, J = 7.8 Hz, 2H, Ar<u>H</u>), 7.32 (t, 1H, ArH), 7.28 (d, J = 7.8 Hz, 2H, Ar<u>H</u>), 7.20 (d, J = 8.4 Hz, 2H, Ar<u>H</u>), 7.19 (t, J = 7.2 Hz, 1H, Ar<u>H</u>), 7.17 (d, J = 9.3 Hz, 2H, Ar<u>H</u>), 7.14 (t, J = 6.6 Hz, 1H, Ar<u>H</u>), 6.99 (t, 1H, Ar<u>H</u>), 6.93 (dd, J = 6.9, 1.5 Hz, 2H, Ar<u>H</u>), 6.86 (dd, J = 7.5, 1.2 Hz, 2H, Ar<u>H</u>), 5.49 (d, J = 3.9 Hz, 1H, <u>H</u>3), 5.35 (d, J = 6.3 Hz, 1H, <u>H</u>5), 4.50 (dd, J = 4.2, 6.3 Hz, 1H, <u>H</u>4), 2.41 (s, 3H, CH₃). ¹³C NMR δ 148.79, 142.82, 139.42, 135.64, 135.59, 134.62, 129.57, 129.22, 128.99, 128.77, 128.59, 128.12, 126.92, 126.76, 126.60, 122.64, 114.85, 84.79, 79.93, 70.21, 21.53. HRMS (CI), calcd for C₃₄H₃₀N₂O₄S₂ 595.17248, found 595.17388. NOESY cross-peaks were observed between Ar₂'ortho' and H3 and H5.

(4c): ¹H NMR δ 7.86 (d, J = 8.1 Hz, 2H, Ar<u>H</u>), 7.73 (d, J = 8.4 Hz, 2H, Ar<u>H</u>), 7.59 (t, J = 7.8 Hz, 1H, Ar<u>H</u>), 7.44 (d, J = 8.1 Hz, 2H, Ar<u>H</u>), 7.41 (m, 2H, Ar<u>H</u>), 7.32 (m, 3H, Ar<u>H</u>), 7.23 (d, J = 7.8 Hz, 2H, Ar<u>H</u>), 7.18 (d, J = 8.7 Hz, 2H, Ar<u>H</u>), 7.16 (t, 1H, Ar<u>H</u>), 7.14 (d, J = 7.8 Hz, 2H, Ar<u>H</u>), 7.00 (t, 1H, Ar<u>H</u>), 6.92-6.86 (dd, 4H, Ar<u>H</u>), 5.80 (d, J = 4.8 Hz, 1H, <u>H</u>3), 4.88 (d, J = 5.7 Hz, 1H, <u>H</u>5), 4.40 (t, J = 5.1 Hz, 1H, <u>H</u>4), 2.41 (s, 3H, CH₃). ¹³C NMR (in part) δ 140.56, 138.32, 137.32, 134.66, 129.66, 129.23, 129.10, 128.90, 128.86, 128.69, 128.54, 128.32, 128.16, 126.98, 126.62, 123.32, 116.12, 84.69, 79.32, 70.99, 21.53. Mass spectrum (ES+) m/z 595.6 (22%, [M+H]+), 338.9 (100).

(3*SR*, 4*SR*, 5*SR*, S*SR*) 2,3,5-Triphenyl-4(*N*-(2,4,6-triisopropylbenzenesulfonyl S-phenylsulfonimidoyl) isoxazolidine (3d) and (3*RS*, 4*RS*, 5*RS*, S*SR*) 2,3,5-Triphenyl-4(*N*-2,4,6-triisopropylbenzenesulfonyl S-phenylsulfonimidoyl) isoxazolidine (4d). The title compounds were obtained from the reaction of the vinyl sulfoximine (1d) (0.10 g, 0.20 mmol) and the nitrone (0.04 g, 0.20 mmol) in CHCl₃ (1.5 mL) at 75-80 °C for 28 days using the general procedure described above. ¹H NMR of the crude reaction mixture showed an diastereomeric ratio of 3 : 1. The reaction was chromatographed on silica gel using ethyl acetate / hexane (1 : 2) as eluent to give 0.096 g (66%) of a mixture of (3d) and (4d). A sample was separated by HPLC using 10% EtOAc / hexane as the mobile phase to give pure samples of (3d) and (4d) as white crystals.

(3d): ¹H NMR δ 7.72 (dd, J = 8.0, 0.8 Hz, 2H, Ar₄ 'ortho'), 7.56 (dd, J = 8.0, 1.6 Hz, 2H, Ar₃ 'ortho'), 7.49 (t, J = 7.6 Hz, 1H, Ar₄ 'para'), 7.34-7.28 (m, 5H, Ar<u>H</u>), 7.21-7.14 (m, 5H, Ar<u>H</u>), 7.05 (s, 2H, Ar₁ 'meta'), 6.97 (dd, J = 8.8, 1.6 Hz, 2H, Ar₅ 'ortho'), 6.96 (t. J = 7.2 Hz, 1H, Ar₂ 'para'), 6.86 (dd, J = 8.8, 0.8 Hz, 2H, Ar₂ 'ortho'), 5.54 (d, J = 4.0 Hz, 1H, <u>H</u>3), 5.38 (d, J = 6.0 Hz, 1H, <u>H</u>5), 4.51 (dd, J = 6.4 0 Hz, 1H, <u>H</u>4), 4.17(quin, 2H, Me₂C<u>H</u>). 2.86 (quin, 1H, Me₂C<u>H</u>), 1.23 (d, J = 6.8 Hz, 6H, C<u>H</u>₃), 1.11 (d, J = 6.4 Hz, 6H, C<u>H</u>₃), 1.08 (d, J = 5.8 Hz, 6H, C<u>H</u>₃). ¹³C NMR δ 152.06, 149.25, 148.78, 139.45, 137.06, 135.99, 135.34, 134.47, 129.36, 129.14, 128.97, 128.95, 128.65, 128.60, 128.07, 127.03, 126.68, 123.31, 122.61, 115.00, 85.29, 80.03, 70.21 34.10, 29.23, 24.68, 23.68, 23.63. Mass spectrum (ES+) m/z 729.4 (100%, [M+Na]⁺), 707.3 (40, [M+H]⁺), 601.3 (30). Anal. Calcd for C₄₂H₄₆N₂O₄S₂: C, 71.14; H, 6.56; N, 3.96. Found C, 71.48; H, 6.67; N, 3.91.

(4d): ¹H NMR δ 7.82 (dd, J = 8.4, 1.2 Hz, 2H, Ar₄ 'ortho'), 7.59-7.57 (d+t, 3H, Ar₄ 'para', Ar₃ 'ortho'), 7.42 (d, J = 8.4 Hz, 2H, Ar₄ 'meta'), 7.38 (d, J = 7.2 Hz, 2H, Ar₁ 'ortho'), 7.36 (t, J = 6.8 Hz, 1H, Ar₃ para'), 7.17-7.12 (t, 2H, Ar₅ 'meta'), t, 1H, Ar₅ 'para'), 7.07 (d, J = 8.0 Hz, 2H, Ar₂ 'meta'), 7.05 (s, 2H, Ar₁ ortho'), 6.97 (t, J = 7.6 Hz, 1H, Ar₂ 'para'), 6.84 (dd, J = 8.8, 1.2 Hz, 2H, Ar₅ 'ortho'), 6.75 (dd, J = 8.4, 1.2 Hz, 2H, Ar₂ 'ortho'), 5.99 (d, 1H, <u>H</u>3), 4.74 (d, 1H, J = 5.4 Hz, <u>H</u>5). 4.45 (dd, 1H, J = 5.4, 4.5 Hz, <u>H</u>4), 4.16 (quin, 2H, Me₂C<u>H</u>), 2.85 (quin, 1H, Me₂C<u>H</u>) 1.22 (d, J = 6.9 Hz, 6H, 2 Me), 1.13 (d, J = 6.6 Hz, 6H, 2 Me), 1.03 (d, J = 6.9 Hz, 6H, 2Me). ¹³C NMR (in part) δ 148.43, 138.32, 138.02, 135.97, 134.54, 129.55, 128.80, 128.76,

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128.70, 128.30, 128.14, 84.85 (C4), 78.35 (C3), 71.12 (C5). Mass spectrum (ES+) m/z 729.2 (54%, [M+Na]⁺) 707.2 (28, [M+H]⁺), 601.1 (20), 287.9 (100).

(3SR, 4SR, 5SR, SSR) 2,3,5-Triphenyl-4(N-methyl S-phenylsulfonimidoyl)isoxazolidine (3e) and

(3RS, 4RS, 5RS, SSR) 2,3,5-Triphenyl-4(*N*-methyl S-phenylsulfonimidoyl)isoxazolidine (4e). The title compounds were obtained from the reaction of the vinyl sulfoximine (1e) (0.209 g, 0.81 mmol) and the nitrone (0.160 g, 0.81 mmol) in CHCl₃ (1.5 mL) at 75-80 °C for 28 days using the general procedure described above. ¹H NMR of the crude reaction mixture showed an diastereomeric ratio of 1 : 1. The reaction was chromatographed on silica gel using 30 % ethyl acetate / hexane as eluent to give 0.160 g (43%) of a mixture of (3e) and (4e). A sample was separated by HPLC using 7.5 % EtOAc / hexane as the mobile phase to give pure samples of (3e) and (4e) as white solids.

(3e): ¹H NMR δ 7.74 (d, 2H, J = 7.5, 1.5 Hz, Ar<u>H</u>), 7.52-7.49 (m, 3H, Ar<u>H</u>), 7.42 (d, J = 7.8 Hz, 2H, Ar<u>H</u>), 7.38-7.13 (m, 9H, Ar<u>H</u>), 7.03-6.93 (m, 4H, Ar<u>H</u>), 5.92 (d, J = 5.4 Hz, 1H, <u>H</u>3), 5.06 (d, J = 5.1 Hz, 1H, <u>H</u>5), 4.29 (t, J = 5.4 Hz, 1H, <u>H</u>4), 2.64 (s, 3H, C<u>H</u>3). ¹³C NMR δ 149.41, 139.79, 138.67, 137.02, 133.11, 129.99. 129.36, 128.75, 128.66. 128.47, 128.09, 127.65, 127.01, 126.80, 122.60, 115.85, 83.74, 79.85, 71.55, 29.71 (NMe), 29.29 (NMe). Mass spectrum (ES+) *m/z* 455 (100%, [M+H]+), 317 (18), 258 (84).

(4e): ¹H NMR δ 7.71-7.63 (m, 4H, Ar<u>H</u>), 7.44-7.22 (m, 8H, Ar<u>H</u>), 7.13 (m, 3H, Ar<u>H</u>), 7.01-6.94 (m, 5H, Ar<u>H</u>), 5.70 (d, J = 3.9 Hz, 1H, <u>H</u>3), 5.36 (d, J = 7.2 Hz, 1H, <u>H</u>5), 4.38 (dd, J = 6.8, 4.0 Hz, 1H, <u>H</u>4), 2.63 (s, 3H, NMe). ¹³C NMR δ 149.66, 141.04, 136.49, 136.26, 133.06, 129.94, 129.22, 128.94, 128.78, 128.39, 127.61, 127.03, 126.98, 122.06, 114.62, 83.65, 81.16, 70.65, 29.69 (NMe) 29.33 (NMe). Mass spectrum (ES+) *m*/z 455.7 (100%, [M+H]⁺), 258.6 (84). HRMS (EI) calcd for C₂₈H₂₆N₂O₂S+H 455.179284 found 455.17934.

References

- (a) Tufariello, J. J. in : 1,3-Dipolar Cycloadditions, Padwa, A., Ed.; Wiley-Interscience: New York, 1984, Vol. 2, Ch. 9. (b) Confalone, P. N.; Huie, E. M. Org. React. 1988, 36, 1.
- 2. Carruthers, W. in: Cycloaddition Reactions in Organic Synthesis, Pergamon, Oxford, 1990, Ch.6.
- (a) Sims, J.; Houk, K. N. J. Am. Chem. Soc. 1973, 95, 5798. (b) De Benedetti, P. G.; Quartieri, S.; Rastelli, A.; De Amici, M.; De Micheli, C.; Ganolfi, R.; Gariboldi, P. J. Chem. Soc. Perkin Trans, II, 1982, 95.
- 4. Koizumi, T.; Hirai, H.; Yoshii, E. J. Org. Chem. 1982, 47, 4005.
- 5. Diels-Alder reactions of vinyl sulfoximines are known: see reference 6.
- 6. Pyne, S. G. Sulfur Reports 1992, 12, 57.
- 7. Dong, Z.; S. G. Pyne, S. G.; B.W. Skelton B. W.; White, A. H. Aust. J. Chem. 1993, 46, 143.
- 8. Johnson, C. R.; Kirchhoff, R. A.; Reischer, R. J.; Katekar, G. F. J. Am. Chem. Soc. 1973, 95, 4287.

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