1,3-Dipolar Cycloaddition Reactions of *trans*-2-Methylene-1,3-dithiolane 1,3-Dioxide with Nitrones

Varinder K. Aggarwal,*,† Richard S. Grainger,† Harry Adams,‡ and Peter L. Spargo§

Department of Chemistry, University of Sheffield, Sheffield S3 7HF, UK, Crystallographic Department, University of Sheffield, Sheffield S3 7HF, UK, and Process R&D Department, Pfizer Central Research, Sandwich, Kent CT13 9NJ, UK

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The 1,3-dipolar cycloaddition reaction between a nitrone and an olefinic dipolarophile is an efficient method for the synthesis of the isoxazolidine ring system (Figure 1).[1] Furthermore, the cycloadducts have found numerous applications in synthesis through reductive cleavage of the N−O bond to give γ-amino alcohols.[1] Asymmetric induction in nitrone−olefin cycloadditions has been achieved through incorporation of chirality in both the dipole and dipolarophile.[2,3] More recently, advances have been made in the use of metals to influence the rate, regioselectivity, stereoselectivity, and enantioselectivity of the reaction through suitable combinations of metal/dipole/dipolarophile, effectively overcoming the tendency of nitrones to form inactive dipole/Lewis acid complexes.[4]

In comparison to the Diels−Alder reaction, the 1,3-dipolar cycloaddition of nitrones with olefins generally exhibits lower levels of regio- and stereocontrol (exo/endo selectivity), a consequence of significant contributions by both LUMO (dipole)−HOMO (dipolarophile) and HOMO (dipole)−LUMO (dipolarophile) interactions, further complicated by the possibility of interconversion of the nitrone geometry in the case of acyclic nitrones.[1] Therefore, despite the advances outlined above, there still remains a need to develop general systems that give predictably high levels of regio- and stereocontrol with a range of nitrones. Herein we describe one potential solution to this problem.

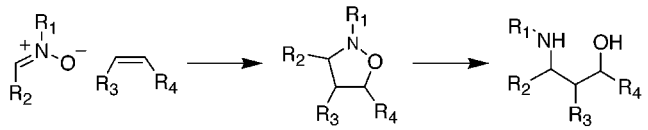

Figure 1.

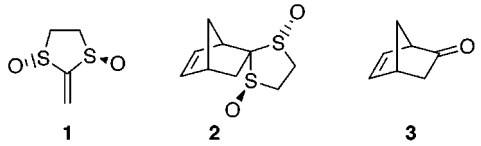

Figure 2.

We have recently reported an asymmetric synthesis of the *C*2-symmetric cyclic alkenyl sulfoxide (1*R*,3*R*)-2-methylene-1,3-dithiolane 1,3-dioxide **1** (Figure 2).[5] The presence of a *C*2 symmetry element in **1** means that the exo/endo approaches of **1** to a diene are symmetry related and therefore identical, thereby reducing the number of competing transition states in the reaction. Indeed, **1** showed very high reactivity and stereoselectivity in Diels−Alder reactions with a range of dienes, and after hydrolysis of the bis-sulfoxide moiety of the cyclopentadiene adduct **2**, enantiomerically pure norbornenone **3** was obtained. Thus, we were able to demonstrate **1** to be an effective chiral ketene equivalent.[5] To the best of our knowledge the potential advantage of using a *C*2-symmetric dipolarophile to overcome the exo/endo issue in 1,3-dipolar cycloaddition chemistry has not been exploited. We report herein our results of the cycloaddition of **1** with some acyclic and cyclic nitrones.

† Department of Chemistry.
‡ Crystallographic Department.
§ Process R&D Department.

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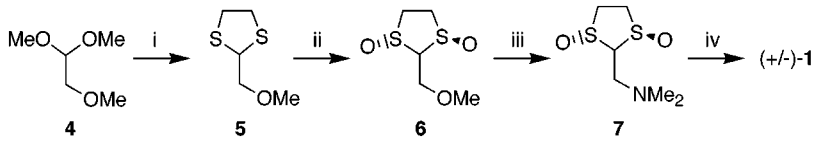
Scheme 1[a]



[a] Reagents and conditions: (i) $HSCH_2CH_2SH$, concd HCl, rt, 6 h (91%); (ii) *m*-CPBA, Et_2O, 0 °C, 2 h (84%); (iii) Me_2NH, MeCN, rt, 24 h (100%); (iv) MeI, *i*-Pr_2NEt, MeCN, rt, 18 h (86%).

Racemic **1** was readily prepared in four steps as outlined in Scheme 1. Transthioketalization of the commercially available acetal **4** with 1,2-ethanedithiol under acid catalysis[6] gave the methoxymethyl-substituted 1,3-dithiolane **5** in high yield. Oxidation of **5** using *m*-CPBA in Et_2O[7] gave exclusively the trans bis-sulfoxide **6** which could be isolated and purified by simple filtration and recrystallization. Compound **6** was smoothly converted to the dimethylamino-derivative **7** simply by stirring in a solution of dimethylamine in acetonitrile at room temperature.[5] Finally, Hofmann elimination using methyl iodide and Hünig's base at room temperature gave **1** in 86% isolated yield.[5]

At the outset of this work it was not clear what the regiochemical preference for the cycloaddition of **1** with nitrones would be. Although vinyl sulfoxides appear to exclusively favor formation of isoxazolidines with the sulfur functionality incorporated at C-4,[8,9] 1,1-disubstituted olefins predominately yield isoxazolidines disubstituted at C-5, the regiochemical preference being influenced more by the substitution pattern on the olefin than by the electronic nature of the substituents.[10] It was therefore gratifying to observe that the cycloaddition of **1** with the commercially available *N*-*tert*-butyl-*C*-phenyl nitrone **8** proceeded readily in dichloromethane at room temperature using 5 equiv of nitrone (the excess nitrone could be recovered) to give a single diastereomeric 4,4-disubstituted isoxazolidine product **11** in 77% isolated yield (Scheme 2, Table 1, entry 1).[11,12] Reaction of **1** with *N*,*C*-diphenyl nitrone **9** and *N*-methyl-*C*-phenyl nitrone **10** proceeded more readily, presumably due to the reduced steric hindrance in these nitrones, to again give single diastereomeric 4-substituted isoxazolidine products **12** and **13**, respectively (Table 1, entries 2, 3).[11]

Scheme 2

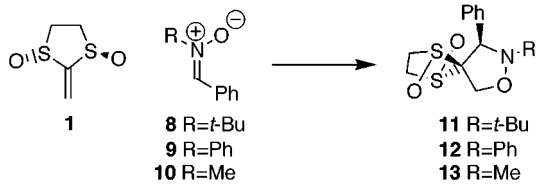


Table 1. 1,3-Dipolar Cycloaddition between 1 and Acyclic Nitrones

entry	nitrone[a]	nitrone adduct	time	isolated yield, %
1	**8**	**11**	48	77
2	**9**	**12**	15	64
3	**10**	**13**	13	86

[a] All reactions were conducted in dichloromethane at room temperature using 5 equiv of nitrone.

The stereochemistry of the *N*-methyl adduct **13** was determined by X-ray crystallography.[13] The observed stereoselectivity can be rationalized by considering the possible transition states for the reaction (Figure 3). Due to the *C*2-symmetry element present in the dipolarophile, only two transition states are possible, leading to the diastereomeric 4-substituted isoxazolidines **13** and **14**. Transition state **TS 1** leads to the observed product **13**. The alternative transition state **TS 2** suffers from steric and/or electronic repulsions between the phenyl ring of the nitrone and the sulfinyl oxygen; in transition state **TS 1** the phenyl group approaches over a sulfinyl lone-pair and the oxygen of the second sulfoxide over the smaller hydrogen atom (Figure 3).[5]

The stereochemical course of the *N*-phenyl and *N*-*tert*-butyl nitrone cycloadditions would be expected to follow a similar pattern. The stereochemistry of isoxazolidines **11** and **12** have thus been assigned by analogy with **13**.[14]

Simple cyclic nitrones are another well-known and frequently studied class of 1,3-dipole. Selectivities in cycloadditions are often much higher than with acyclic

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(10) (a) Reference 1. (b) For an example see: Keirs, D.; Moffat, D.; Overton, K.; Tomanek, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1041−1051. (c) Brandi has frequently observed significant amounts of the 4-substituted isomer in his use of methylene cyclopropanes as dipolarophiles in 1,3-dipolar cycloadditions: Brandi, A.; Cordero, F. M.; De Sarlo, F.; Goti, A.; Guarna, A. *Synlett* **1993**, 1−8. Attempts to rationalise this selectivity by an FMO treatment gave unsatisfactory results: Brandi, A.; Cordero, F. M.; Desarlo, F.; Gandolfi, R.; Rastelli, A.; Bagatti, M. *Tetrahedron* **1992**, *48*, 3323−3334. There are a few examples of the nitrone cycloaddition of 1,1-disubstituted alkenes bearing electron-withdrawing groups (diethyl methylenemalonate). Selective formation of 4,4-disubstituted isoxazolidines is observed with N,C-diphenyl nitrone and with 2,3,4,5-tetrahydropyridine 1-oxide but *N*-methyl nitrone gives the 5,5-disubstituted isoxazolidine instead. See: Ali, S. A.; Senaratne, P. A.; Illig, C. R.; Meckler, H.; Tufariello, J. J. *Tetrahedron Lett.* **1979**, *20*, 4167−4170.

(11) No other adduct could be detected by TLC or in the crude NMR of the reaction mixture.

(12) Yields of nitrone cycloadducts have not been optimized.

(13) The author has deposited atomic coordinates for **13** and **19a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.

(14) This transition state argument assumes nitrones **8**−**10** react through their *Z*-form, as they exist at the reaction temperature. However, the same major product could also be obtained via an *E*-nitrone and applying a similar argument. Although the nitrones would not be expected to interconvert between *Z*- and *E*-forms at room temperature, the greater reactivity of *E*-nitrones over *Z*-nitrones means that the possibility of this interconversion during the reaction cannot be ignored. See for example ref 3h.

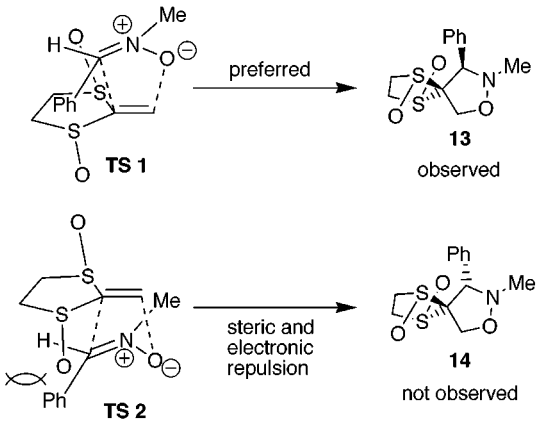

Figure 3.

Table 2. 1,3-Dipolar Cycloaddition between 1 and Cyclic Nitrones

entry	nitrone[a]	*T* (°C)	time	nitrone adducts	ratio of adducts (**a**:**b**)[b]	isolated yield, %
1	**15**	−78	60 min	**18a:18b**	22:1	84
2	**16**	−78	60 min	**19a:19b**	20:1	75
3	**17**	rt	48 h	**20**	−	81

[a] All reactions were conducted in dichloromethane using 5 equiv of nitrone. [b] Determined by ^{1}H NMR integration of crude reaction mixtures.

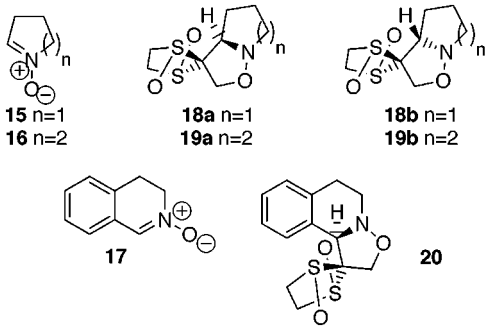

Figure 4.

nitrones due to the absence of *E*−*Z* isomerization in the dipole. Furthermore, with nonconjugated monosubstituted olefins, reactions have been shown to proceed preferentially via exo-transition states affording trans-adducts; endo-transition states are disfavored by steric interactions of substituents on the dipolarophile with methylene groups on the ring.[1] It was of interest therefore to investigate how a 1,1-disubstituted dipolarophile such as **1**, in which one substituent must always interact to some extent with the dipole ring, would react with such nitrones.

The results of the 1,3-dipolar cycloaddition of **1** with nitrones **15**−**17** are summarized in Table 2. Reaction with the pyrrolidine-derived nitrone **15** occurred readily at room-temperature giving a 10:1 mixture of **18a**:**18b** (Figure 4). Assignment of the minor isomer as diastereomer **18b** rather than a regioisomer was based upon the NMR of the (inseparable) mixture of cycloadducts. The geminal protons of the isoxazolidine ring appear as simple doublets for both major and minor products. The greater reactivity of the cyclic nitrones over their acyclic counterparts allowed this reaction to occur at lower temperature. After only 60 min at −78 °C, all alkene **1** had been consumed, and the cycloadduct was isolated as

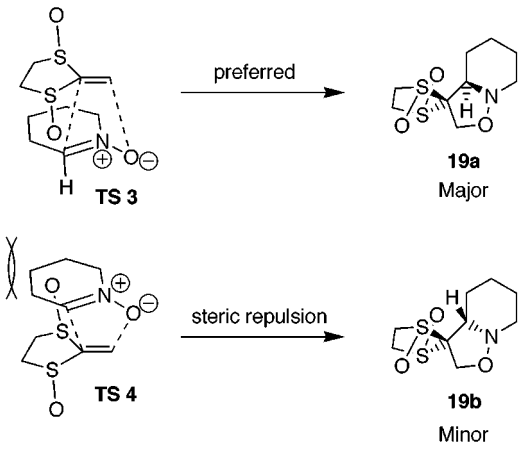

Figure 5.

a 22:1 mixture of diastereomers (entry 1). Similarly, the diastereomeric ratio obtained from reaction of nitrone **16** with **1** could be increased from 10:1 at room temperature to 20:1 at −78 °C (entry 2). **1** underwent completely regio- and stereoselective cycloaddition with the isoquinoline-derived nitrone **17** (entry 3). The stereochemistry of isoxazolidine **20** (and of the major adduct **18a**) was assigned as shown by analogy with **19a** (*vide infra*, *vide supra*).

Slow recrystallization of a mixture of **19a** and **19b** allowed for the unambiguous determination of the structure of the major adduct **19a** by X-ray crystallography.[13] Based upon this crystal structure, a stereochemical rationale can again be proposed. The two possible transition states leading to the two diastereomeric isoxazolidines **19a** and **19b** are shown in Figure 5. To account for the observed selectivity, transition state **TS 3** must be favored over transition state **TS 4**. Presumably the unfavorable steric interactions in **TS 3** are even more pronounced in **TS 4,** where the "offending" oxygen approaches over the bulk, rather than the periphery, of the nitrone ring. The higher selectivity observed in the case of **17** may be due to an additional electronic repulsion in transition state **TS 4** between the sulfinyl−oxygen lone pair and the π-system of the aromatic ring.[5]

In conclusion we have reported that the *C*2-symmetric dipolarophile **1** adds to both acyclic and cyclic nitrones with very high stereoselectivity. In addition, the 1,3-dipolar cycloaddition of **1** with nitrones is a rare example of a 1,1-disubstituted olefin reacting regioselectively to give 4,4- rather than 5,5-disubstituted isoxazolidines.

Experimental Section

General. *m*-CPBA was purified by washing an ether solution of commercially available material (57−86%) four times with a phosphate buffer, followed by drying and careful removal of solvent. Nitrone **10** was prepared by the condensation of *N*-methylhydroxylamine and benzaldehyde according to the method of DeShong.[15] Nitrones **15**−**17** were prepared in one step from the corresponding amine through treatment with hydrogen peroxide in the presence of a tungstate catalyst according to Murahashi.[16] All other reagents are commercially available and were used as received.

(15) Dicken, C. M.; DeShong, P. *J. Org. Chem.* **1982**, *47*, 2047−2051.
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2-(Methoxymethyl)-1,3-dithiolane (5). A 1 L three-necked RB flask equipped with a 250 cm^3 pressure-equalizing dropping funnel, thermometer, and overhead stirrer was charged with 1,2-ethanedithiol (91 cm^3, 1.095 mol) and concentrated hydrochloric acid (77 cm^3). The mixture was cooled to 0 °C, and 2-methoxyacetaldehyde dimethyl acetal **4** (131 cm^3, 1.03 mol) was slowly added via the dropping funnel over 1.5 h, ensuring the temperature did not rise above 10 °C. The reaction mixture was stirred for a further 1 h at 0 °C and then 3 h at room temperature. The reaction mixture was partitioned between dichloromethane (200 cm^3) and H_2O (200 cm^3), the organic phase separated, and the aqueous phase extracted with more dichloromethane (200 cm^3). Combined organics were washed with water (200 cm^3), saturated $NaHCO_3$ solution (300 cm^3), and brine (200 cm^3) and dried over $MgSO_4$, and solvent was removed under reduced pressure. Distillation of the liquid residue gave the *title compound* as a colorless liquid (140.5 g, 91%), bp 54−55 °C (0.15 mmHg), (Found: C, 39.6; H, 6.8; S, 43.1%. $C_5H_{10}S_2O$ requires C, 40.0; H, 6.7; S, 42.7%); υ_{max}(thin film)/cm^{-1} 2980−2820; ^{1}H NMR (250 MHz; $CDCl_3$) δ 3.19 (4H, s), 3.39 (3H, s); 3.47 (2H, d, J = 7) and 4.58 (1H, t, J = 7); ^{13}C NMR (63 MHz; $CDCl_3$) δ 38.0, 51.4, 48.9 and 77.6; m/z (EI) 150 (M^+, 100%).

(1*RS*,3*RS*)-2-(Methoxymethyl)-1,3-dithiolane 1,3-Dioxide (6). 1,3-Dithiolane **5** (15.99 g, 106 mmol) was dissolved in dry ether (300 cm^3) and the temperature reduced to 0 °C. A solution of purified *m*-CPBA (40 g, 232 mmol) in dry ether (400 cm^3) was added dropwise over 1 h, and then the reaction mixture was stirred for a further 1 h at 0 °C. The resulting white precipitate was filtered and washed with cold ether. Recrystallization from hot ethyl acetate gave white crystals of the *title compound* (16.13 g, 84%), R_f 0.3 (10% MeOH/EtOAc), mp 124−125 °C (EtOAc), (Found: C, 32.8; H, 5.3; S, 35.3%. $C_5H_{10}S_2O_3$ requires C, 32.95; H, 5.5; S, 35.2%); υ_{max}(KBr)/cm^{-1} 2975−2830 and 1020 (S═O); ^{1}H NMR (300 MHz; $CDCl_3$) δ (single diastereomer) 3.43 (3H, s), 3.60−3.82 (4H, m) and 3.90−4.10 (3H, m); δ_C (63 MHz; $CDCl_3$) 51.3 and 51.8, 59.5, 64.2 and 89.5; m/z (EI) 183 (MH^+, 100%).

(1*RS*,3*RS*)-2-[(Dimethylamino)methyl]-1,3-dithiolane 1,3-Dioxide (7). (1*RS*,3*RS*)-2-(Methoxymethyl)-1,3-dithiolane 1,3-dioxide **6** (1.44 g, 7.92 mmol) was dissolved in a solution of dimethylamine in acetonitrile (25 cm^3, 0.3 M) at room temperature. The solution was stirred in the dark for 24 h, after which time acetonitrile, excess dimethylamine, and liberated methanol were evaporated under reduced pressure to give the *title compound* as an off white solid (1.54 g, 100%), R_f 0.3 (5% MeOH/acetone), mp 105.5−106.5 °C(*t*-BuOAc); (Found: C, 36.8; H, 6.9; N, 7.2; S, 32.5%. $C_6H_{13}NS_2O_2$ requires C, 36.9; H, 6.7; N, 7.2; S, 32.8%); υ_{max}(KBr)/cm^{-1} 1028 (S═O); ^{1}H NMR (250 MHz; $CDCl_3$) δ 2.37 (6H, s), 2.91 (2H, d, J = 8.5), 3.50−3.83 (4H, m) and 3.92 (1H, td, J = 8.5 and 0.6); ^{13}C NMR (63 MHz; $CDCl_3$) δ 45.5, 50.8, 51.3 and 52.1 and 90.5; m/z (EI) 195 (M^+, 24%), 118 (55) and 58 (100).

(1*RS*,3*RS*)-2-Methylene-1,3-dithiolane 1,3-Dioxide (1). Amine **7** (531.6 mg, 2.72 mmol) was dissolved in dry acetonitrile (5.4 cm^3) at room temperature under nitrogen. *N*,*N*-Diisopropylethylamine (0.95 cm^3, 5.44 mmol) was added followed by methyl iodide (0.85 cm^3, 13.61 mmol). After 2 min the reaction mixture turned cloudy. The solution was stirred at room temperature for a further 18 h. Dry EtOAc (11 cm^3) was then added and the reaction mixture filtered. The precipitate (diisopropylethylmethylammonium iodide and tetramethylammonium iodide) was washed with more EtOAc (4 × 5.5 cm^3) and the filtrate evaporated under reduced pressure. Flash column chromotography on Sorbsil silica[17] C60 (40−60 um), eluting with acetone, gave diisopropylethylammonium iodide followed by the *title compound* as a white solid (351.4 mg, 86%), R_f 0.4 (5% MeOH/acetone), (Found: C, 32.2; H, 4.0%; S, 42.4. $C_4H_6S_2O_2$ requires C, 32.0; H, 4.0; S, 42.6%); υ_{max}(KBr)/cm^{-1}1630 and 1030; ^{1}H NMR (250 MHz; $CDCl_3$) δ 3.60−3.82 (4H, m) and 6.91 (2H, s); δ_C (63 MHz, $CDCl_3$) 51.4, 135.4 and 165; m/z (EI) 150 (M^+, 47%), 122 (23), 108 (43) and 58 (100).

(1*RS*,3*RS*,3′*RS*)-2′-*tert*-Butyl-3′-phenylspiro[(1,3-dithiolane)-2,4′-isoxazolane] 1,3-Dioxide (11). *N*-*tert*-Butyl-*C*-phenyl nitrone **8** (354 mg, 2 mmol) was added in one portion to a solution of alkene **1** (59 mg, 0.4 mmol) in dry dichloromethane (0.8 cm^3) at room temperature under nitrogen. After stirring for 48 h, the reaction mixture was columned directly, eluting with ethyl acetate. The excess nitrone eluted first, followed by the *title compound* as a white solid (99 mg, 77%), R_f 0.5 (EtOAc), mp 149.5−150 °C (EtOAc), (Found: C, 55.0; H, 6.4; N, 4.4; S, 19.7%. $C_{15}H_{21}S_2O_3N$ requires C, 55.0; H, 6.5; N, 4.3; S, 19.6%); υ_{max}(KBr)/cm^{-1} 3063−2868, 1051 and 1032 (S═O); ^{1}H NMR (250 MHz; $CDCl_3$) δ 1.08 (9H, s), 3.24 (1H, dt, J = 14 and 4.5), 3.34 (1H, ddd, J = 14, 4.5 and 2), 3.69 (1H, ddd, J = 14, 4.5 and 2), 3.82 (1H, dt, J = 14 and 4.5); 3.99 (1H, d, J = 11.5), 4.61 (1H, d, J = 11.5), 4.93 (1H, s), 7.96 (1H, br d, J = 7.5) and 7.01−7.49 (4H, m); ^{13}C NMR (63 MHz; $CDCl_3$) δ 26.2, 50.9, 51.3, 59.7, 61.0, 67.9, 103.1, 127.3, 128.3, 128.7, 129.1, 129.2 and 138.8; m/z (EI) 327 (M^+, 9), 310 (12), 254 (17), 250 (15), 194 (100), 146 (19), 115 (21), 104 (41), 77 (27) and 57 (64%); (Found: M^+, 327.0957. $C_{15}H_{21}S_2O_3N$ requires m/z, 327.0963).

(1*RS*,3*RS*,3′*RS*)-2′,3′-Diphenylspiro[(1,3-dithiolane)-2,4′-isoxazolidine] 1,3-Dioxide (12). *N*,*C*-Diphenyl nitrone **9** (483 mg, 2.45 mmol) was added in one portion to a solution of alkene **1** (71.4 mg, 0.47 mmol) in dry dichloromethane (0.95 cm^3) at room temperature under nitrogen. After stirring the resulting suspension for 15 h, the white solid (undissolved nitrone) was filtered and the filtrate evaporated under reduced pressure. Column chromatography, eluting with ethyl acetate, gave excess nitrone, followed by the *title compound* as an off-white solid (105.3 mg, 64%), R_f 0.4 (EtOAc), mp 139−140 °C (yellow crystals, EtOAc/40−60 petroleum ether), (Found: C, 58.6; H, 4.9; N, 4.1; S, 18.5%. $C_{17}H_{17}S_2O_3N$ requires C, 58.8; H, 4.9; N, 4.0; S, 18.45%); υ_{max}(KBr)/cm^{-1} 3060−2937, 1596, 1488, 1038; ^{1}H NMR (250 MHz; $CDCl_3$) δ 3.24−3.45 (2H, m), 3.61−3.78 (2H, m), 4.29 (1H, d, J = 11), 4.86 (1H, d, J = 11), 5.37 (1H, s), 6.98−7.07 (3H, m), 7.20−7.44 (5H, m) and 7.56−7.64 (2H, m); ^{13}C NMR (63 MHz; $CDCl_3$) δ 51.2, 51.3, 67.6, 68.8, 102.7, 116.3, 123.5, 128.1, 128.9, 129.0, 129.2, 135.5 and 148.6; m/z (EI) 347 (M^+, 7), 330 (5), 270 (53), 223 (19), 193 (21), 180 (100), 149 (63) and 77 (52%); (Found: M^+, 347.0642. $C_{17}H_{17}S_2O_3N$ requires m/z, 347.0650).

(1*RS*,3*RS*,3′*RS*)-2′-Methyl-3′-phenylspiro[(1,3-dithiolane)-2,4′-isoxazolidine] 1,3-Dioxide (13). *N*-Methyl-*C*-phenyl nitrone **10** (2.391 g, 17.7 mmol) was added in one portion to a solution of alkene **1** (539 mg, 3.6 mmol) in dry dichloromethane (7.2 cm^3) at room temperature under nitrogen. After stirring for 13 h the reaction mixture was subjected to column chromatography on silica gel, eluting with ethyl acetate. The *title compound* was obtained as a white solid (879 mg, 86%), R_f 0.4 (EtOAc), mp 140−140.5 °C (EtOAc), (Found: C, 50.1; H, 5.2; N, 4.95; S, 22.3%. $C_{12}H_{15}S_2O_3N$ requires C, 50.5; H, 5.3; N, 4.9; S, 22.5%); υ_{max}(KBr)/cm^{-1} 3056−2932, 1491, 1054 and 1030; ^{1}H NMR (250 MHz; $CDCl_3$) δ 2.74 (3H, s), 3.09 (1H, dt, J = 14 and 5), 3.37 (1H, ddd, J = 14, 4 and 2), 3.64 (1H, ddd, J = 14, 5 and 2), 3.76 (1H, dt, J = 14 and 4), 4.09 (1H, d, J = 11), 4.39 (1H, s), 4.65 (1H, d, J = 11), 7.25−7.38 (3H, m) and 7.46−7.56 (2H, m); ^{13}C NMR (63 MHz; $CDCl_3$) δ 42.9, 51.4, 51.7, 68.4, 72.3, 99.9, 128.7, 128.9, 129.0, and 132.5; m/z (EI) 285 (M^+, 8), 268 (25), 208 (63), 134 (25), 118 (100) and 77 (43%); (Found: M^+, 285.0489. $C_{12}H_{15}S_2O_3N$ requires m/z, 285.0493).

(1*RS*,3*RS*,3a′*RS*)-Spiro[(1,3-dithiolane)-2,3′-perhydropyrrolo[1,2-*b*]isoxazole] 1,3-Dioxide (18a). Alkene **1** (64 mg, 0.43 mmol) was added to a solution of 1-pyrroline *N*-oxide **15** (180 mg, 2.1 mmol) in dry dichloromethane (0.84 cm^3) at −78 °C under nitrogen. After stirring for 1 h, the solution was allowed to warm to room temperature. Column chromatography of the reaction mixture, eluting with neat acetone, gave cycloadducts **18a** and **18b** together as an approximately 22:1 mixture of diastereomers (74 mg, 75%). Recrystallization from ethyl acetate/40−60 petroleum ether gave the *title compound* as white crystals (68 mg, 69%), R_f 0.4 (acetone), mp 127−128 °C (EtOAc/40−60 petroleum ether), (Found: C, 40.8; H, 5.5; N, 6.0; S, 27.45%. $C_8H_{13}S_2O_3N$ requires C, 40.8; H, 5.6; N, 5.95; S, 27.25%); υ_{max}(KBr)/cm^{-1} 2986−2950, 1056 and 1042; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.84−1.95 (1H, m), 2.00−2.23 (3H, m), 3.13 (1H, dt, J = 13.5 and 7.5), 3.36−3.40 (1H, ddd, J = 13.5, 7.5 and 5), 3.45 (1H, dt, J = 14 and 4.5), 3.57 (1H, ddd, J = 14, 4.5 and 1.5), 3.65 (1H, ddd, J = 14, 4.5, 1.5), 3.83 (1H, dt, J = 14 and 4.5), 3.86 (1H, d, J = 10.5), 4.09 (1H, t, J = 8) and 4.50 (1H,

(17) It is essential to use this grade silica. Merck silica gel 60, eluting with distilled acetone, caused some decomposition and transformation of the product into the *bis*-sulfoxide **6**. We do not know the origin of the methanol.

d, $J = 10.5$); ^{13}C NMR (63 MHz; $CDCl_3$) δ 25.0, 28.5, 50.4, 51.4, 56.0, 64.7, 66.0 and 100.9; *m*/*z* (EI) 235 (M^+, 14), 218 (29), 158 (100), 112 (48), 85 (24), 68 (28) and 55 (23%); (Found: M^+, 235.0301. $C_8H_{13}S_2O_3N$ requires *m*/*z*, 235.0337).

Peaks assignable to minor diastereomer **18b**: δ_H (250 MHz; $CDCl_3$) 3.95−4.05 (1H, m), 4.41 (1H, d, $J = 10$).

(1*RS*,3*RS*,3a′*RS*)-Spiro[(1,3-dithiolane)-2,3′-perhydroisoxazolo[2,3-*a*]pyridine] 1,3-Dioxide (19a). Alkene **1** (67 mg, 0.45 mmol) was added to a solution of 2,3,4,5-tetrahydopyridine *N*-oxide **16** (248 mg, 2.5 mmol) in dry dichloromethane (0.89 cm^3) at −78 °C under nitrogen. After stirring for 1 h, the solution was allowed to warm to room temperature. Column chromatography of the reaction mixture, eluting with ethanol−ethyl acetate (1:10) gave cycloadducts **19a** and **19b** together as an approximately 20:1 mixture of diastereomers (94 mg, 84%). Slow recrystallization from CH_2Cl_2 gave crystals of the *title compound*, R_f 0.4 (10% EtOH/EtOAc), mp 154−155 °C (EtOAc), (Found: C, 43.3; H, 5.9; N, 5.7; S, 25.6%. $C_9H_{15}S_2O_3N$ requires C, 43.35; H, 6.1; N, 5.6; S, 25.7%); υ_{max}(KBr)/cm^{-1} 2956−2826 and 1036; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.21−1.35 (1H, m), 1.57−1.90 (5H, m), 2.56 (1H, ddd, $J = 3$, 9 and 12), 2.94 (1H, dd, $J = 11.5$ and 2.5), 3.46−3.58 (2H, m), 3.63−3.79 (3H, m), 3.90 (1H, d, $J = 11$) and 4.43 (1H, d, $J = 11$); ^{13}C NMR (63 MHz; $CDCl_3$) δ 23.3, 24.2, 26.1, 51.1, 52.0, 55.5, 64.2, 70.6 and 96.6; *m*/*z* (EI) 249 (M^+, 12), 232 (28), 172 (83), 150 (30), 126 (26), 108 (26), 99 (54), 82 (49), 58 (100), 55 (48%); (Found: M^+, 249.0492. $C_9H_{15}S_2O_3N$ requires *m*/*z*, 249.0493).

(1*RS*,3*RS*,3a′*RS*)-Spiro[(1,3-dithiolane)-2,1′-1′,5″,6′10b-tetrahydro-2′*H*-isoxazolo[3,2-*a*]isoquinoline] 1,3-Dioxide (20). Alkene **1** (544 mg, 3.6 mmol) was added in one portion to a solution of 3,4-dihydroisoquinoline *N*-oxide **17** (2.67 g, 18.1 mmol) in dry dichloromethane (7.2 cm^3) under nitrogen at room temperature. The homogeneous orange solution was stirred for a further 48 h and then preabsorbed onto silica gel. Column chromatography, eluting with neat ethyl acetate, gave the *title compound* as a white solid (870 mg, 81%), R_f 0.3 (EtOAc), mp 124−125 °C (EtOAc), (Found: C, 52.5; H, 5.05; N, 4.8, 21.4%. $C_{13}H_{15}S_2O_3N$ requires C, 52.5; H, 5.1; N, 4.7, S, 21.6%); υ_{max}(KBr)/cm^{-1} 3020 (C-H aromatic), 2967−2847, 1492, 1042; ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.91−3.04 (1H, m), 3.10−3.23 (2H, m), 3.28−3.34 (1H, m), 3.46 (1H, dt, $J = 13.5$ and 4), 3.53 (1H, ddd, $J = 14$, 4 and 1.5), 3.65 (1H, dt, $J = 14$ and 4), 3.73 (1H, ddd, $J = 14$, 4 and 1.5), 4.08 (1H, d, $J = 11.5$), 4.73 (1H, d, $J = 11.5$), 5.27 (1H, s), 7.13−7.26 (3H, m) and 7.46−7.50 (1H, m); ^{13}C NMR (63 MHz; $CDCl_3$) δ 28.7, 47.4, 51.1, 52.9, 66.3, 66.8, 99.9, 127.1, 127.6, 128.1, 128.7, 129.0 and 133.9; *m*/*z* (EI) 297 (M^+, 10), 220 (6), 147 (100), 130 (23), 115 (27), 91 (40) and 58 (73%); (Found: M^+, 297.0488. $C_{13}H_{15}S_2O_3N$ requires *m*/*z*, 297.0493).

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Supporting Information Available: X-ray data including ORTEP drawing of **13** and **19a** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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