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1,3-Dipolar cycloaddition of nitrones with phenylvinyl sulfone. An experimental and theoretical study

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ABSTRACT

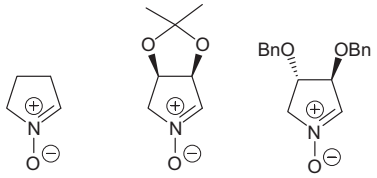
The addition of three nitrones to phenylvinylsulfone, **1**, has been studied. The stereochemistry previously established by two-dimensional NMR techniques was confirmed by X-ray crystal structure determination. Theoretical studies made us propose that this reaction is not purely regioselective, but by controlling the substituents of nitrone and temperature the regioselectivity increases.

1. Introduction

The 1,3-dipolar cycloaddition is one of the most useful reactions in organic synthesis.[1] Many dipoles and dipolarophiles have been employed to obtain either carbocycles or heterocycles. It is worth mentioning that nitrones have been successfully employed to produce aza-heterocycles such as isoxazolidines in a simple manner.[2] The 1,3-dipolar cycloaddition of nitrones derived from pyrrolidine compounds to different dipolarophiles has been an essential transformation in the synthesis of pyrrolidines, pyrrolizidines, and indolizidines because of the important role of these ring systems in many natural products with physiological activity.[3] Although the intermolecular cycloaddition of nitrones with alkenes has been extensively studied, the corresponding reaction of nitrones with phenylvinylsulfones has received little attention.[4]

Recently, there has been a renewed interest in the crystallography of sulfones,[5] thus we decided to study the cycloaddition of several nitrones with a commercially available sulfone. Herein the behavior of three nitrones (Fig. 1), which has been previously studied in cycloaddition reactions to obtain biologically active compounds[3] with phenylvinylsulfone **1** is disclosed. This sulfone has been employed to obtain isoxazolidines, but always with open chain nitrones.[6]

Nitrone, **2**, has been obtained as described by Brandi and Cordero et al.[7] Chiral nitrone **3**, has been synthesized according to the procedure of Goti et al.[3c] Finally nitrone **4**, was obtained starting from diethyl tartrate according to the procedure of Brandi et al.[8]



2 **3** **4**

Figure 1. Nitrones employed in the study.

2. Results and discussion

Our study began with the 1,3-dipolar cycloaddition reaction of chiral nitrone **3** with phenylvinylsulfone in different solvents and under conditions as shown in Table 2. We selected nitrone **3** because it has been used extensively by others for the synthesis of many biologically active compounds,[3b,c,g] and the possibility that the resulting isoxazolidines would be crystalline. As a consequence, it was possible to easily establish unequivocally the stereochemistry of the final adducts. When **3** was reacted with phenylvinylsulfone **1** in toluene, the four isoxazolidines **5a–5d** were obtained (Scheme 1).

The structure of these compounds was established by one and two-dimensional NMR experiments. The assignments of all the hydrogens and carbons are included in the Experimental. The hydrogen coupling constants, especially H3 and H3a (Table 1), were essential for the determination of the stereochemistry. Compounds **5a–5d** were all crystalline and it was possible to confirm their structures unequivocally by single crystal X-ray diffraction (Fig. 2).[9]

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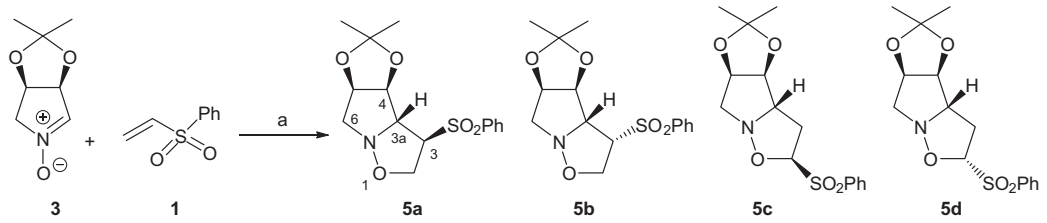


Scheme 1. Reaction of nitrone **3** with phenyl vinyl sulfone **1**. See Table 2.

Table 1
Coupling constants for isoxazolidines **5a–5d**

J (Hz)	5a	5b	5c	5d
H2α–H3	7.6	8.7	—	—
H2β–H3	5.6	8.7	—	—
H2α–H2 β	7.6	8.7	—	—
H2–H3α	—	—	8.8	7.4
H2–H3β	—	—	3.8	7.4
H3α–H3β	—	—	13.6	13.6
H3–H3a	5.6	8.7	—	—
H3α–H3a	—	—	5.8	7.4
H3β–H3a	—	—	7.6	7.4
H3a–H4	1.8	2.6	2.6	1.8
H4–H5	6.2	6.6	6.2	6.6
H5–H6α	6.2	5.6	5.6	5.6
H5–H6β	3.0	3.0	3.6	2.6
H6α–H6β	13.2	13.2	13.8	13.2

See numbering of compounds in Scheme 1.

Table 2
Solvent and temperature conditions effect in the reaction of nitrone **3**, with phenylvinylsulfone **1**

Entry	Solvent	T^a (°C)	*t* (h)	Yield	Additive	Ratio%			
						5a	5b	5c	5d
1	THF	25	16	76		35	32	19	14
2	THF	−78	7	27		27	26	16	31
3	DCM	25	4	77		33	33	11	24
4	DCM	−78	6	30		32	32	11	26
5	Toluene	25	6	98		38	38	13	13
6	Toluene	25	24	80	HMPA	23	27	31	19
7	Toluene	−78	7	26		24	23	13	41
8	Toluene	85	12	89		23	47	17	12

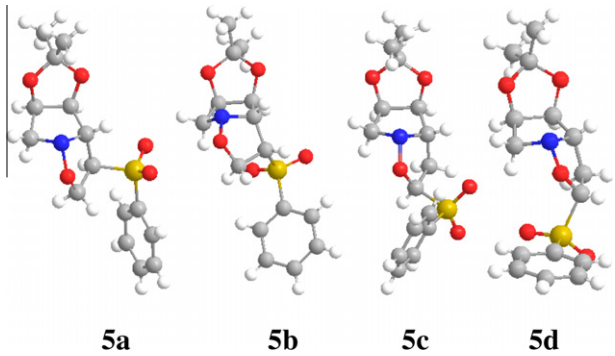
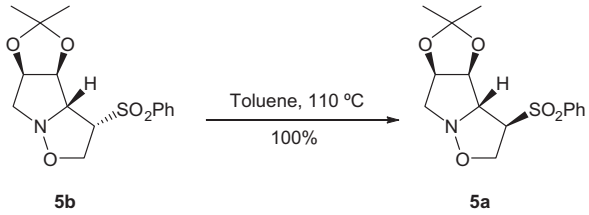


Figure 2. X-ray crystal structures for compounds **5a–5d**.

As can be seen from Table 2, the stereochemistry of the addition occurs *anti* with respect to the acetonide group. Isoxazolidines are mainly obtained with the sulfonyl group in the 3-position and there is no special *endo*/*exo* selectivity. When the reaction is performed in the presence of a coordinating agent (entry 6) the regioselectivity of the reaction changes though not the *endo*/*exo* ratio. In order to investigate the possibility of a retrocycloaddition we submitted separately compounds **5a–5d** into the same cycloaddition conditions. We only observed a conversion in quantitative yield of **5b** into **5a**; all the rest were recovered without change. (Scheme 2).



Scheme 2. Conversion of **5b** into **5a**.

Having obtained the best yields with toluene at 25 °C, we chose these conditions to study the 1,3-dipolar cycloaddition with the other nitrones. Our results are shown in Scheme 3 and Table 3.

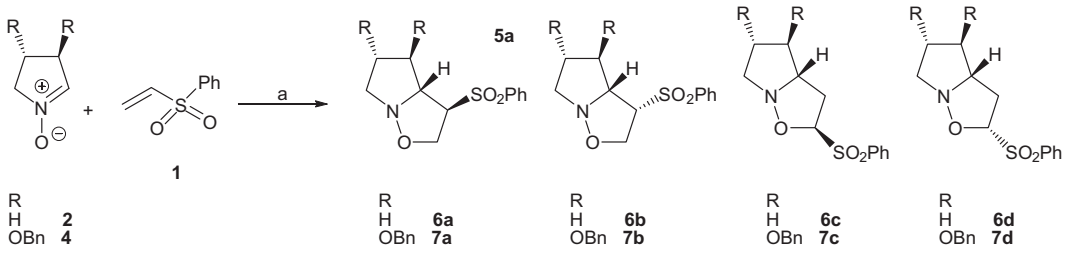
It was observed (Table 3, entry 1) that nitrone **2** reacts with phenylvinylsulfone with no regio- or stereoselectivity. In the case of nitrone **4**, entry 2, the same facial selectivity as nitrone **3** is observed: the addition is *anti* to the benzyl group in the 3-position of nitrone. Nitrone **4** is less regioselective and shows the opposite preference to nitrone **3** (Table 2, entry 5). Under the same conditions, the proportion **5a** + **5b** is bigger than **7c** + **7d** for nitrone **3** than for nitrone **4**.

In order to explain the experimental results, including the regiochemistry, diastereoselectivity, and kinetic control, we undertook a theoretical study of these dipolar cycloadditions. Although there is a considerable background of theoretical studies about 1,3-dipolar cycloadditions in which nitrones are involved as dipoles,[10] and a wide variety of dipolarophiles have been checked, surprisingly there are only a few examples of computational investigations with α,β-unsaturated sulfones.[11]

Mechanistic details such as regiochemistry, synchronicity, and *endo*/*exo* ratios for this type of cycloaddition with nitrones have been long discussed.[11b] Regiochemistry depends on the nature of the dipolarophile; the *endo*/*exo* adducts ratio is related to the size of both reactants, and the synchronicity is the result of several system and environmental factors. Because of the nature of the environment of the reactions (solvents rather apolar and aprotic), a concerted cycloaddition mechanism was assumed.

3. Computational details

All the calculations were performed in Jaguar v. 7.6.[12] Molecular minimizations of reactants, products, and transition states were carried out with Density Functional Theory (DFT) using Becke's[13] three-parameter hybrid exchange (B3) with the Lee-Yang-Parr's[14] (LYP) correlation functional (B3LYP). Although the use of B3LYP for transition states has been shown to be rather effective, there are some cases where the results are not reliable.[15] Particularly in the light of recent papers by Houk, showing that B3LYP may not be the functional of choice for 4+2 cycloadditions,[16] we've also



Scheme 3. Reaction of nitrones **1** and **4** with phenylvinyl sulfone.

Table 3
Isoxazolidines obtained from reaction of nitrones **2** and **4** with phenylvinyl sulfone **1**

Entry	Nitrone	T^a (°C)	t (h)	Yield	Isoxazolidines			
					a	**b**	**c**	**d**
1	**2**	25	6	38	1.1	1.3	1.0	1.1
2	**4**	25	6	45	1.2	1.0	2.5	Not observed

performed single point calculations with M05-2X[17] over B3LYP optimized geometries with ultrafine grid (UF), which has been demonstrated to be a more realistic method.[15] 6-31G*[18] basis set has been chosen to perform the calculations because it provides good correlation with experimental data.[19] Transition state search was performed through Linear Synchronous Transit (LST), after those geometry optimizations using the same theory level was achieved. As the best yields of the reactions were obtained in toluene, additional environmental effects were taken into account through PBF[20] solvent model, using toluene's dielectric constant at 298 K, $\varepsilon = 2.34$. Posterior vibrational normal mode analysis was carried out to verify that reactants and products were stationary points (zero imaginary frequencies) and transition structures had one and only one imaginary frequency. Quick reaction coordinate (QRC)[21] was used for each transition structure to check that they were on the pathway from reactants to products, rather than suggesting a different mechanism. Thermodynamic data were extracted from vibration analysis and scaling factors were not applied.

3.1. Computational analysis of reactants

Structures of phenylvinylsulfone **1** and nitrones **2**, **3** were minimized according with the parameters described. After that, frontier molecular orbital (FMO) analysis and global/local reactivity indexes were used to predict regioselectivity. Figure 3 shows FMO interactions of phenylvinylsulfone **1** with nitrones **2** and **3**. It is clear that the electron density transfer takes place from the HOMO orbitals of nitrones to LUMO orbital of phenylvinylsulfone, as a result of the small energy gap (normal electron demand character). This is supported with the global reactivity indexes summarized in Table 4. Electronic chemical potential is defined as the mean value of HOMO and LUMO energies [$\mu = (\varepsilon_{HOMO} + \varepsilon_{LUMO})/2$] and is a relative measure of the molecular capacity to donate electron density, while the global electrophilicity index is the ratio $\omega = \mu^2/(2\eta)$, which measures the total ability to attract electrons. η is the chemical hardness, and is the difference between the HOMO and LUMO energies [$\eta = (\varepsilon_{LUMO} - \varepsilon_{HOMO})$].

Dipoles **2**–**3** have an electronic chemical potential higher than sulfone, which means that the electronic flow is again from the nitrone type dipoles to sulfone **1** as dipolarophile. Although the chemical hardness of the three species involved are almost the same, phenylvinylsulfone possesses a high electrophilicity, so it has more potential to experience nucleophilic attacks than its dipole counterparts.

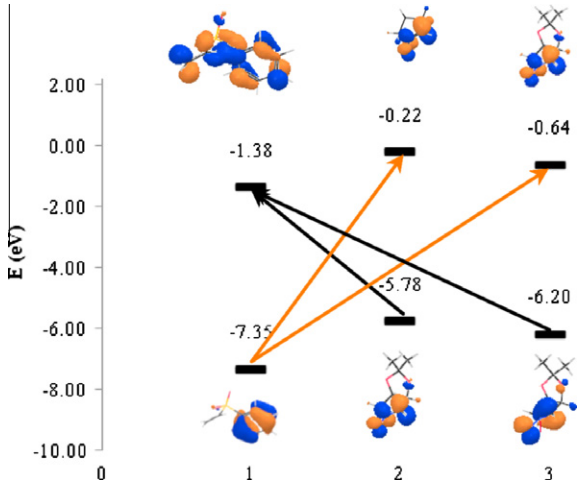


Figure 3. Frontier molecular orbitals from sulfone **1** and nitrones **2** and **3**.

Table 4
HOMO/LUMO energies, electronic chemical potential, chemical hardness and global electrophilicity index of reactants (in a.u.)

Molecule	HOMO	LUMO	μ	η	ω
1	−0.270	−0.051	−0.160	0.219	0.058
2	−0.228	−0.024	−0.126	0.204	0.038
3	−0.212	−0.008	−0.110	0.204	0.029

After evaluating the global nucleophilic/electrophilic character, a local analysis was carried out through Fukui indices calculation. Fukui functions are defined as $f^+_k = \rho_k(N+1) - \rho_k(N)$ and $f^-_k = \rho_k(N) - \rho_k(N-1)$, for LUMO/HOMO electron density variation. Thus, electrophilicity local indices are calculated from Fukui parameters $\omega_k^{\pm} = \omega f^{\pm}$. As we can see in Table 5, the preferred two center interactions take place between centers O1–C1 and C2–C3, leading to a 3-phenylsulfonyl isoxazolidine regiochemistry.

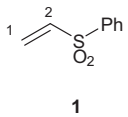
In summary, preliminary analysis of the reactants lead to two ideas: (i) Nitrones act as nucleophiles and sulfones **1** as electrophiles, (ii) the most favorable attack takes places from the O1 of nitrones to C1 of sulfone, leading to a 3-phenylvinyl isoxazolidine as the major regioisomer.

3.2. Computational analysis of the reactions

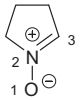
The theoretical study of the reactants lead to an explanation for the regiochemistry. Transition states and reaction pathways were investigated next. Tables 6 and 7 and Figures 5 and 6 summarized the energy and geometric and thermodynamic parameters together with energy profiles of the reaction between **1** and **3**.

Figure 5 shows relative free energy profiles of the different pathways toward isoxazolidine products, differentiating regiochemical

Table 5
Fukui functions and local electrophilicity indexes for the centers of the species involved in the 1,3-dipolar cycloaddition



1



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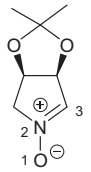


3

	Sulfone **1**		Nitrone **2**		Nitrone **3**	
	C1	C2	O1	C3	O1	C3
f+	0.229	0.124	0.164	0.449	0.180	0.405
f−	0.014	0.010	0.521	0.344	0.500	0.366
ω+	0.014	0.007	0.006	0.018	0.005	0.012
ω−	0.001	0.001	0.020	0.013	0.015	0.011

routes employing B3LYP/6-31G* theory and M05-2X(UF)/6-31G*//B3LYP/6-31G*. According to the B3LYP/6-31G* results, **5b** pathway is the most favorable line of reaction both in the gas phase and surrounded by a toluene Poisson-Boltzmann Finite (PBF) type environment, with a difference of 2 kcal/mol in solvent with respect to the next transition level (Table 6). Furthermore, comparing the molecular gas phase and solution energies is remarkable that in gas phase the second favorable pathway is to **5d**, while in a solvated system, **5a** is as favorable as **5d**. This observation suggests that in the gas phase the *endo* approach is more important than regiochemistry, as a consequence of secondary orbital interaction between HOMO and LUMO, which is comparable to solvation effects forward. In **5b**, this interaction takes place between H of nitrone **3** and O of sulfone **1**, while in **5d**, the interaction is localized as a lateral interaction between HOMO and LUMO, as a result of the extension of the latter along the sulfone group (Fig. 4).

Table 6 presents thermodynamic data for the structures studied. Rate constants were calculated according with the Eyring transition state theory:

$$k = \frac{Tk_B}{h} e^{\left(-\frac{\Delta G^{\ddagger}}{RT}\right)} \quad (1)$$

where k_B is Boltzmann's constant; h is Planck's constant; R is the ideal gas constant; T is the temperature (25 °C), and, $\Delta G^{\ddagger}$ is the relative Gibbs energy of the transition state structures. It is interesting to note that the activation enthalpies for **TS-5a** and **TS-5b** are slightly lower than other intermediates with B3LYP functional, but the **TS-5b** enthalpy according to M05-2X theory is much lower almost 6 kcal/mol. Moreover, the activation entropies in both theories are similar, with no special differences between channels. This results in a small Gibbs activation energy of the 3-phenylsulphonyl isoxazolidine pathway **5b**, as a consequence of the minimum entropy effect on different channels and a dominance of the enthalpy term, which are plotted in Figure 5.

Rate constants were calculated to compare experimental and theoretical results, suggesting that the major product should be **5b**, with the other isomers forming to a much lesser extent. One reason of this discrepancy between theoretical and experimental results might be the type of functional used; therefore single point calculations on each of the gas phase optimized structures with the M05-2X functional under an ultrafine grid (UF), together with the PBF solvation model, was envisaged as has been described previously. The results show no new differences, keeping the **5b** channel as the only product. However, the corresponding energies of the products are lower than the B3LYP model, showing that a possible backward process would be energetically more demanding than the direct cycloaddition.

From these results, we conclude that the theoretical behaviors are far from the experimental results, which imply that there is a competition between kinetic and thermodynamic effects and Eyring theory does not completely cover the study. The reaction energy studies compared with the experimental data suggest that at lower temperatures the reaction is not a pure cycloaddition and could take place in two steps: Michael addition and then cyclization.

Another interesting feature is that when the four cycloaddition products were heated in toluene separately only **5b** turns into **5a** (Scheme 2); the rest did not exhibit any transformation. This fact is consistent with the idea that these reactions are thermally irreversible, as a consequence of the greater activation energy (between 23 and 28 kcal/mol for B3LYP, 32–41 kcal/mol for M05-2X)

Table 6
Relative enthalpies (kcal/mol), entropies (cal/K/mol) and Gibbs energies (kcal/mol) in solution at 298 K

Reaction	Species	(PBF)B3LYP/6-31G*						(PBF)M05-2X(UF)/6-31G*//B3LYP/6-31G*					
		ΔH^{α}	ΔS^{α}	ΔG^{α}	$k_{(25)}$	k_{rel}	%	ΔH^{α}	ΔS^{α}	ΔG^{α}	$k_{(25)}$	k_{rel}	%
1 + 3	**TS-5a**	13.59	−42.35	26.21	3.72×10^{-7}	30	2	8.91	−50.38	23.94	1.74×10^{-5}	1	0
	TS-5b	11.03	−42.94	23.83	1.90×10^{-5}	1700	98	1.20	−51.01	16.41	5.76	331693	100
	TS-5c	14.10	−47.36	28.22	9.03×10^{-8}	1	0	7.86	−49.71	22.68	1.44×10^{-4}	8	0
	TS-5d	14.13	−43.13	26.98	1.11×10^{-8}	8	0	7.31	−50.29	22.31	2.72×10^{-4}	16	0
	5a	−17.45	−52.60	−1.78				−32.95	−52.47	−17.30			
	5b	−16.32	−52.94	−0.54				−31.77	−53.24	−15.90			
	5c	−20.75	−56.97	−3.77				−31.23	−51.71	−15.81			
	5d	−18.63	−37.83	−7.36				−35.25	−52.19	−19.69			

Transition structures are listed with theoretical rate constants (in s^{-1}) and relative ratio to **5c**. PBF-B3LYP/6-31G(d) and M05-2X (UF)/6-31G*//B3LYP/6-31G* theories.

Table 7
Bond distances, bond differences and bond final distance average (in Ångstrom) of the minimized structures

Reaction	Species	d(O1–C1)	d(C2–C3)	Δd(O1–C1)	Δd(C2–C3)	%	
1 + 3	**TS-5a**	2.021	2.239	0.577	0.685	40	44
	TS-5b	1.841	2.326	0.421	0.786	30	51
	TS-5c	2.074	2.188	0.689	0.647	50	42
	TS-5d	2.199	2.090	0.803	0.559	58	37
	5a	1.444	1.554				
	5b	1.420	1.540				
	5c	1.385	1.541				
	5d	1.396	1.531				

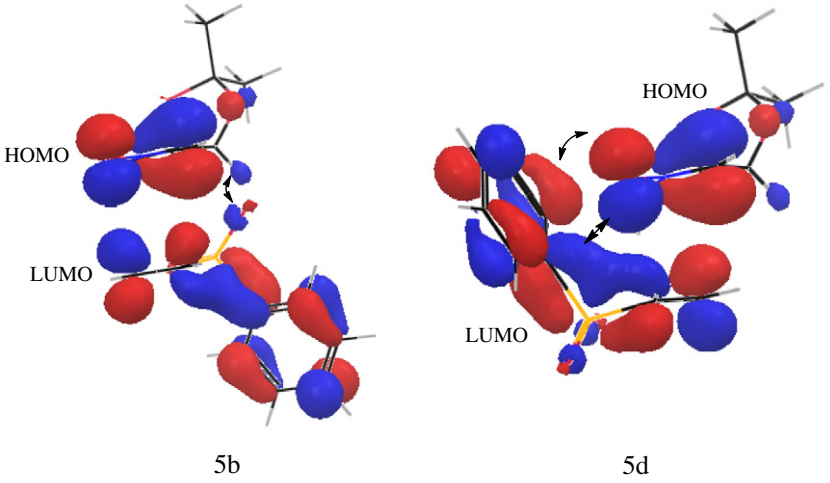


Figure 4. Detail of secondary orbital interaction for intermediates **5b** and **5d**.

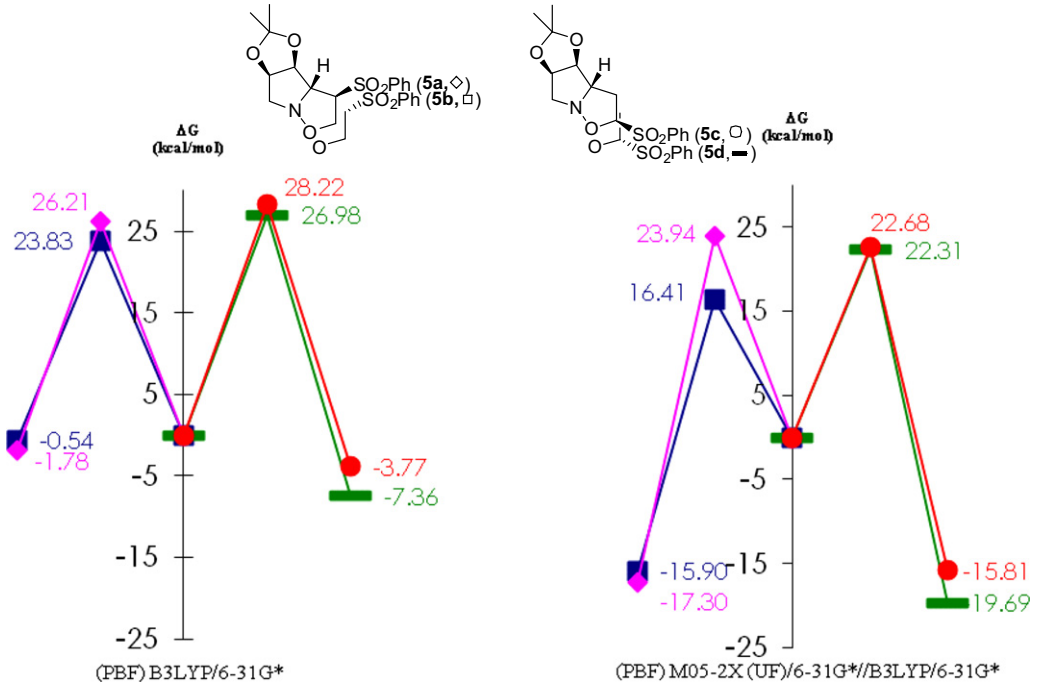


Figure 5. Free energy reaction profiles of the 1,3-dipolar cycloadditions of nitrone **3** with phenylvinylsulfone **1** using B3LYP/6-31G(d) theory (left) and M05-2X (UF)/6-31G*//B3LYP/6-31G* theory (right), both with a PBF solvation model.

for the possible cycloreversion reactions. If these barriers were lower, a mixture of the four products would be obtained. For this reason, the mechanism of the interconversion is in agreement with an epimerization type reaction through the betaine intermediate **I** (Scheme 4). This outcome would explain a theoretical increase in **5a**, due to the involvement of this epimerization after the cycloaddition.

Figure 6 shows geometrical parameters of the bonds of the five centers involved in the isoxazolidine ring formation.

Table 7 shows bond lengths of the transition structures and stationary points, and difference between each state. To check the synchronicity of the reactions, average difference between transition bond structures and products were calculated.

As can be seen, these 1,3 dipolar cycloadditions are slightly asynchronous, due to the small difference between both distances. It is interesting that in pathways **a**/**b** the O1–C1 bond formation is more advanced, while in pathways **c**/**d** it is more delayed. This is reflected by the Fukui indices: in the first case (a most favorable interaction) and a small repulsive interaction between oxygen of the nitrone and oxygen of the sulfone group in the latter. Local reactivity indexes also explain that the least synchronous transition state **5b** led also to the lowest activation barrier, as a result of the most favorable interactions. The lower synchronicity of the reaction, the further from a cyclic electron density flow and, consequently, electron density is more localized and a weaker stabilization is seen in non-polar solvents such as toluene. This could be the reason why the transition structure **5b** has the weakest solvent stabilization and **5a** has the strongest.

The following reaction profiles between phenylvinylsulfone **1** and nitrone **2** was realized. Results are summarized in Tables 8 and 9 and Figures 7 and 8.

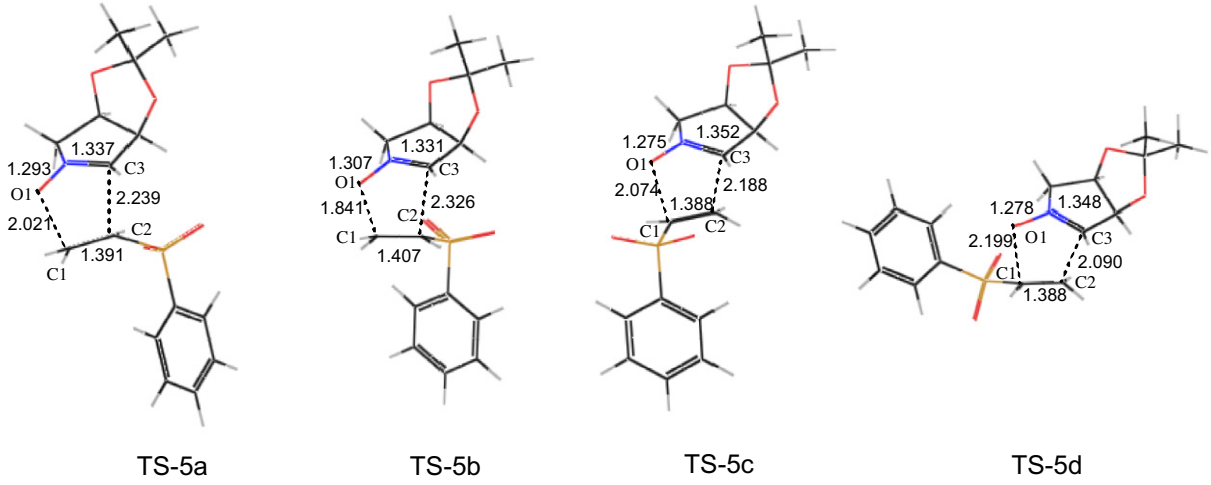
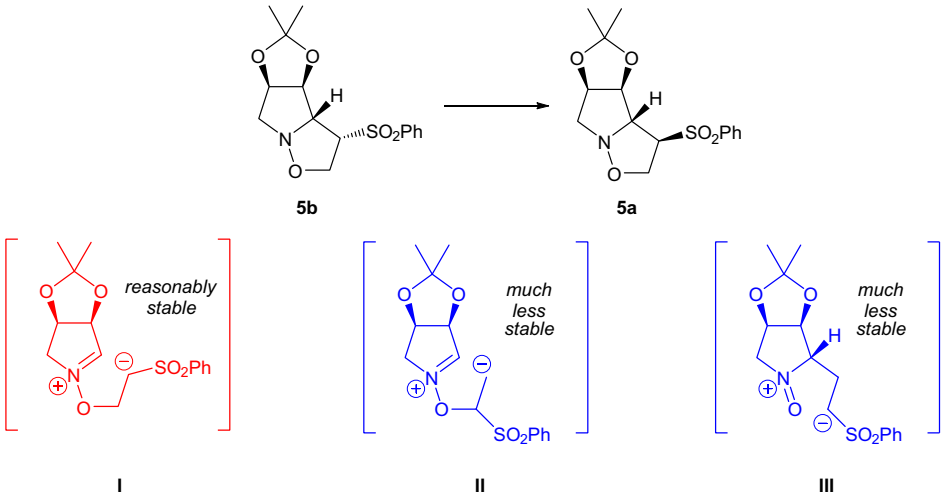


Figure 6. Transition structures of the dipolar cycloaddition reaction between sulfone **1** and nitrone **3**. Bond lengths of selected bonds are in Ångstrom.



Scheme 4. Probable betaine intermediates in the conversion of **5b** to **5a**.

Table 8
Relative enthalpies, Gibbs energies (both in kcal/mol) and entropies (cal/mol) in solution at 298 K

Reaction	Species	(PBF)B3LYP/6-31G*						(PBF)M05-2X(UF)/6-31G*//B3LYP/6-31G*					
		ΔH^{α}	ΔS^{α}	ΔG^{α}	$k_{(25)}$	k_{rel}	%	ΔH^{α}	ΔS^{α}	ΔG^{α}	$k_{(25)}$	k_{rel}	%
1 + 2	**TS-6a**	12.10	−46.25	25.89	6.41×10^{-7}	25	16	3.18	−48.86	17.75	0.6	4182	9
	TS-6b	11.08	−46.48	24.94	3.21×10^{-6}	123	82	1.68	−49.29	16.38	6.07	42,292	91
	TS-6c	14.39	−45.73	28.02	1.75×10^{-8}	1	0	7.83	−48.56	22.31	2.70×10^{-4}	2	0
	TS-6d	13.55	−47.77	27.79	2.61×10^{-8}	1	1	6.99	−49.21	21.67	8.02×10^{-4}	6	0
	6a	−10.37	−48.20	3.99				−24.66	−50.82	−9.51			
	6b	−8.32	−49.79	6.52				−23.18	−51.36	−7.87			
	6c	−9.84	−48.80	4.71				−23.11	−51.07	−7.88			
	6d	−12.37	−55.88	4.28				−25.22	−50.87	−10.05			

Transition structures are listed together with negative imaginaries frequencies and theoretical rate constants (in s^{-1}).

Once again, according to the B3LYP functional used, the **6b** route is the most favorable reaction pathway, both in the gas phase and solution. However, the difference between this route and the next one, **6a**, is smaller than the previous case. Another interesting aspect is the preference toward **6a**/**6b** pathways and no great endo approach selectivity. This is significant, because the dioxolane group has a weak second order interaction between HOMO and LUMO and this interaction is not present for unsubstituted **2**.

Table 8 and Figure 7 show thermodynamic data for the four routes and the relative energy profile of the **1** + **2** dipolar cycloaddition. Channels **6a**/**6b** show as well a low activation enthalpy compared with the rest, and activation entropies of these channels are slightly less negative (B3LYP). Differences between Gibbs activation energies are smaller than the previous case (about 1 kcal/mol between energy levels). Rate constant calculations show again that **6b** is the more favorable product. As far as M05-2X

Table 9
Bond distances, bond differences and bond final distance average (in Ångstrom) of the minimized structures

Reaction	Species	*d*(O1–C1)	*d*(C2–C3)	Δ*d*(O1–C1)	Δ*d*(C2–C3)	%	
1 + **2**	**TS-6a**	1.879	2.313	0.446	0.783	31	51
	TS-6b	1.797	2.366	0.366	0.826	26	54
	TS-6c	2.167	2.073	0.751	0.550	53	36
	TS-6d	2.201	2.056	0.784	0.531	55	35
	6a	1.433	1.530				
	6b	1.431	1.540				
	6c	1.416	1.523				
	6d	1.417	1.525				

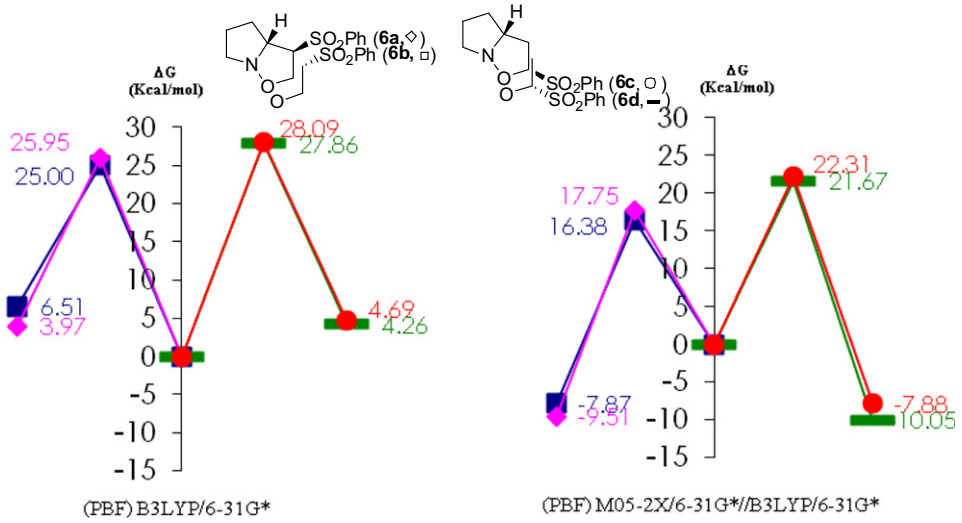


Figure 7. Free energy reaction profiles of the 1,3-dipolar cycloadditions of nitrone **2** with phenylvinylsulfone **1** using B3LYP/6-31G(d) theory (left) and M05-2X (UF)/6-31G*//B3LYP/6-31G* theory (right), both with PBF solvation model.

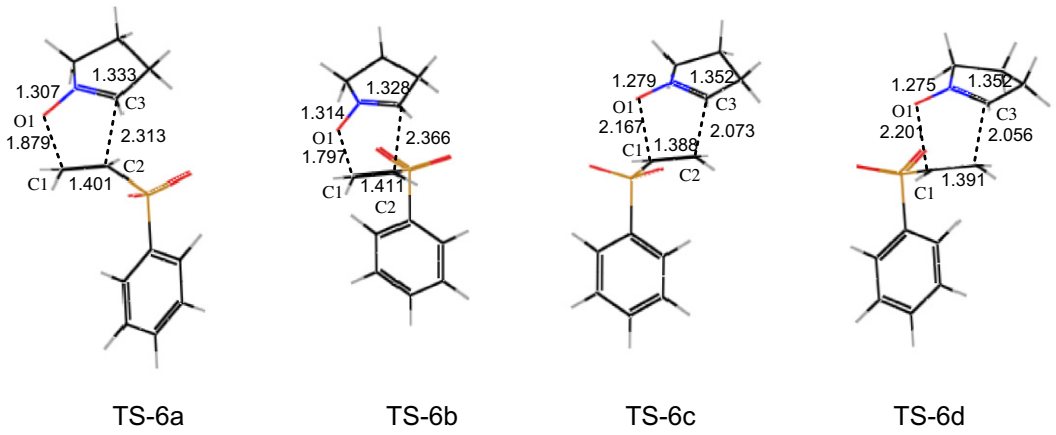


Figure 8. Transition structures of the dipolar cycloaddition reaction between sulfone **1** and nitrone **2**. Bond lengths of selected bonds are in Ångstrom.

calculations are concerned, **6b** is again the dominant reaction pathway, due to the enthalpy value. And besides, the relative Gibbs energy of the products is now negative, diminishing the previously B3LYP values in a similar fashion to the backward reaction. This is more realistic since the reaction at room temperature is spontaneous: M05-2X predicts endergonic reactions, while B3LYP supports exergonic processes.

Figure 8 and Table 9 show geometrical parameters of the bonds of the five atoms involved in the cycloaddition between **1** and **2**, together with the synchronicity parameters of the reactions.

The data reveal similar conclusions to the initial cycloaddition study of **1**+**3**, although this cycloaddition is less synchronous.

In summary, reaction of nitrones **2** and **3** with phenylvinylsulfone **1** in toluene as solvent results in a mixture of diastereoisomers, in which the major product is from the *endo* approach which leads to a 3-phenylsulfonylisoxazolidines **5b** and **6b**, followed by the other diastereoisomers **5a** and **6a**. However, the transition state results suggest that the selectivity should be much higher than that observed experimentally. This may be indicative of additional processes that were not considered by the calculations, such as alternative pathways or a different spin state. The conversion between **5b** to **5a** shows a very interesting behavior of this system, and might compensate the large difference between epimers due to a consecutive reaction. Alternatively, it may be an indication

that the level of theory used (PBF-B3LYP/6-31G(d)) is insufficiently accurate to compare the competing reactions in these cases. Single point M05-2X calculations led to the same conclusions, but improving the endergonic character of the reactions, corresponding with the experimental behavior of these systems at 25 °C.

4. Conclusions

The 1,3-dipolar cycloadditions of phenylvinylsulfone and several nitrones have been studied both experimentally and theoretically, showing that this reaction is not perfectly regioselective, but, by controlling the substituents of nitrone and temperature, the regioselectivity can be biased toward the 3-phenylisoxazolidine products. X-ray structures and the coupling constants are given for several isoxazolidines that will help in the structural determination of analogue compounds.

5. Experimental section

5.1. General

Unless otherwise stated, all chemicals were purchased as the highest purity commercially available and were used without further purification. IR spectra were recorded on a BOMEM 100 FT-IR or an AVATAR 370 FT-IR Thermo Nicolet spectrophotometers. ^{1}H and ^{13}C NMR spectra were performed in $CDCl_3$ and referenced to the residual peak of $CHCl_3$ at δ 7.26 ppm and δ 77.0 ppm, for ^{1}H and ^{13}C, respectively, using Varian 200 VX and Bruker DRX 400 instruments. Chemical shifts are reported in δ ppm and coupling constants (J) are given in Hertz. MS were performed at a VG-TS 250 spectrometer at 70 eV ionizing voltage. Mass spectra are presented as m/z (% rel int.). HRMS were recorded on a VG Platform (Fisons) spectrometer using chemical ionization (ammonia as gas) or Fast Atom Bombardment (FAB) technique. For some of the samples, QSTAR XL spectrometer was employed for electrospray ionization (ESI). Optical rotations were determined on a Perkin-Elmer 241 polarimeter in 1 dm cells. THF were distilled from sodium, and dichloromethane was distilled from calcium hydride under argon atmosphere.

5.2. Cycloaddition of nitrone 3 to phenyl vinyl sulfone 1

Table 2, entry 1: Phenyl vinyl sulfone **1** (64 mg, 0.39 mmol) was added to a solution of nitrone **3** (40 mg, 0.26 mmol) in THF (1 mL) at rt. The resulting mixture was stirred for 16 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **5a**, **5b**, **5c,** and **5d** in 76% combined yield.

Table 2, entry 2: Phenyl vinyl sulfone **1** (58.6 mg, 0.35 mmol) was added to a solution of nitrone **3** (45.6 mg, 0.29 mmol) in THF (1 mL) at −78 °C. The resulting mixture was stirred for 7 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **5a**, **5b**, **5c,** and **5d** in 27% combined yield.

Table 2, entry 3: Phenyl vinyl sulfone **1** (25.4 mg, 0.15 mmol) was added to a solution of nitrone **3** (18.4 mg, 0.12 mmol) in DCM (0.5 mL) at rt. The resulting mixture was stirred for 4 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **5a**, **5b**, **5c,** and **5d** in 77% combined yield.

Table 2, entry 4: Phenyl vinyl sulfone **1** (72.6 mg, 0.43 mmol) was added to a solution of nitrone **3** (56.5 mg, 0.35 mmol) in DCM (1.2 mL) at −78 °C. The resulting mixture was stirred for 6 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **5a**, **5b**, **5c,** and **5d** in 30% combined yield.

Table 2, entry 5: Phenyl vinyl sulfone **1** (536 mg, 3.18 mmol) was added to a solution of nitrone **3** (400 mg, 2.54 mmol) in toluene (8.5 mL) at rt. The resulting mixture was stirred for 6 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **5a**, **5b**, **5c,** and **5d** in 98% combined yield. Ratio Table 2.

Table 2, entry 6: 1.0 equiv HMPA with respect to phenylvinylsulfone **1** was added.

Table 2, entry 7: Phenyl vinyl sulfone **1** (62.4 mg, 0.37 mmol) was added to a solution of nitrone **3** (46.6 mg, 0.29 mmol) in toluene (1 mL) at −78 °C. The resulting mixture was stirred for 7 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **5a**, **5b**, **5c,** and **5d** in 26% combined yield.

Table 2, entry 8: To a stirred solution of nitrone **3** (125 mg, 0.78 mmol) in toluene (4 mL), phenyl vinyl sulfone **1** (160 mg, 0.94 mmol) was added and the mixture was heated at 85 °C. After 12 h the reaction was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **5a**, **5b**, **5c** and **5d** in 89% combined yield.

5.2.1. (3*R*,3a*R*,4*S*,5*R*)-3-Phenylsulfonyl-4,5-isopropylidenedioxyhexahydropyrrolo[1,2-*b*]isoxazole 5a

$[\alpha]_D^{20} = +11.2$ (c 0.7, $CHCl_3$); IR (film) ν: 3440, 2983, 2925 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.96 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.71 (t, ^3J (H,H) = 7.4 Hz, 1H), 7.63 (t, ^3J (H,H) = 7.2 Hz, 2H), 4.84 (dt, ^3J (H,H) = 2.8, 6.2 Hz, 1H), 4.50 (dd, ^3J (H,H) = 1.8, 6.2 Hz, 1H), 4.20 (d, ^3J (H,H) = 7.6 Hz, 1H), 4.05 (dd, ^3J (H,H) = 1.8, 5.6 Hz, 1H), 3.91 (dd, ^3J (H,H) = 5.6, 7.6 Hz, 1H), 3.33 (dd, ^3J (H,H) = 2.8, 13.2 Hz, 1H), 3.17 (dd, ^3J (H,H) = 6.2, 13.2 Hz, 1H), 1.47 (s, 3H), 1.25 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 137.5, 134.4, 129.6, 128.7, 113.1, 83.5, 79.6, 72.6, 70.3, 66.1, 59.2, 26.4, 24.8 ppm; HRMS (EI) $C_{15}H_{19}NO_5S$ requires (M+Na) 348. 0876; found 348.0868.

5.2.2. (3*S*,3a*R*,4*S*,5*R*)-3-Phenylsulfonyl-4,5-isopropylidenedioxyhexahydropyrrolo[1,2-*b*]isoxazole 5b

$[\alpha]_D^{20} = +22.5$ (c 1.4, $CHCl_3$); IR (film) ν: 3457, 2987, 2921, 1315, 1156 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.96 (d, ^3J (H,H) = 8.2 Hz, 2H), 7.70 (t, ^3J (H,H) = 7.6 Hz, 1H), 7.60 (t, ^3J (H,H) = 7.4 Hz, 2H), 5.64 (dd, ^3J (H,H) = 2.6, 6.6 Hz, 1H), 5.02 (ddd, ^3J (H,H) = 3.0, 5.6, 6.6 Hz, 1H), 4.29 (t, ^3J (H,H) = 8.7 Hz, 1H), 4.21 (t, ^3J (H,H) = 8.7 Hz, 1H), 3.91 (dd, ^3J (H,H) = 2.6, 8.7 Hz, 1H), 3.89 (t, ^3J (H,H) = 8.7 Hz, 1H), 3.44 (dd, ^3J (H,H) = 5.6, 13.2 Hz, 1H),

3.30 (dd, ^3J (H,H) = 3.0, 13.2 Hz, 1H), 1.50 (s, 3H), 1.37 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 139.5, 134.3, 129.6, 128.0, 112.7, 80.2, 79.0, 72.9, 68.4, 65.9, 58.7, 26.7, 24.8 ppm; HRMS (EI) $C_{15}H_{19}NO_5S$ requires (M+Na) 348. 0876; found 348.0868.

5.2.3. (2*R*,3a*S*,4*S*,5*R*)-2-Phenylsulfonyl-4,5-isopropylidenedioxy-hexahydropyrrolo[1,2-*b*]isoxazole 5c

$[\alpha]_D^{20} = +155.0$ (*c* 0.9, $CHCl_3$); IR (film) *v*: 3379, 2987, 2905, 1438, 1389, 1299 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.97 (d, ^3J (H,H) = 7.6 Hz, 2H), 7.64 (t, ^3J (H,H) = 7.8 Hz, 1H), 7.62 (t, ^3J (H,H) = 7.4 Hz, 2H), 5.02 (dd, ^3J (H,H) = 3.8, 8.8 Hz, 1H), 4.86 (m, H-5, 1H), 4.55 (dd, ^3J (H,H) = 2.6, 6.2 Hz, 1H), 3.85 (ddd, ^3J (H,H) = 2.6, 5.8, 8.0 Hz, 1H), 3.38 (dd, ^3J (H,H) = 3.6, 13.8 Hz, 1H), 3.31 (dd, ^3J (H,H) = 5.6, 13.8 Hz, 1H), 3.22 (ddd, ^3J (H,H) = 3.8, 7.6, 13.6 Hz, 1H), 2.60 (ddd, ^3J (H,H) = 5.8, 8.8, 13.6 Hz, 1H), 1.48 (s, 3H), 1.28 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 136.0, 134.2, 129.1, 129.0, 113.4, 92.0, 83.9, 80.3, 70.9, 61.5, 33.6, 26.7, 24.8 ppm; HRMS (EI) $C_{15}H_{19}NO_5S$ requires (M+Na) 348. 0876; found 348.0868.

5.2.4. (2*S*,3a*S*,4*S*,5*R*)-2-Phenylsulfonyl-4,5-isopropylidenedioxy-hexahydropyrrolo[1,2-*b*]isoxazole 5d

$[\alpha]_D^{20} = -130.5$ (*c* 1.6, $CHCl_3$); IR (film) *v*: 3475. 2935. 1310. 1149. 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.97 (d, ^3J (H,H) = 7.4 Hz, 2H), 7.64 (t, ^3J (H,H) = 7.8 Hz, 1H), 7.62 (t, ^3J (H,H) = 7.4 Hz, 2H), 4.99 (ddd, ^3J (H,H) = 2.6, 5.6, 6.6 Hz, 1H), 4.95 (d, ^3J (H,H) = 7.4 Hz, 1H), 4.74 (dd, ^3J (H,H) = 1.8, 6.6 Hz, 1H), 3.92 (dt, ^3J (H,H) = 7.4, 1.8 Hz, 1H), 3.70 (dd, ^3J (H,H) = 5.6, 13.2 Hz, 1H), 3.45 (dd, ^3J (H,H) = 2.6, 13.2 Hz, 1H), 2.88 (ddd, ^3J (H,H) = 7.9, 8.0, 15 Hz, 1H), 2.80 (dt, ^3J (H,H) = 13.6, 7.4 Hz, 1H), 1.48 (s, 3H), 1.28 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 136.8, 134.3, 129.2, 129.1, 112.5, 94.0, 81.9, 79.7, 71.5, 61.1, 39.9, 26.5, 24.9 ppm; HRMS (EI) $C_{15}H_{19}NO_5S$ requires (M+Na) 348. 0876; found 348.0865.

5.3. Cycloaddition of nitrone 2 to phenyl vinyl sulfone 1

Table 3, entry 1: Phenyl vinyl sulfone **1** (5 g, 29.4 mmol) was added to a solution of nitrone **2** (2 g, 23.5 mmol) in toluene (75 mL) at rt. The resulting mixture was stirred for 6 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **6a**, **6b**, **6c,** and **6d** in a 38% yield. Ratio Table 3.

5.3.1. (3*R**,3a*R**)-3-Phenylsulfonyl–hexahydropyrrolo[1,2-*b*]-isoxazole 6a

IR (film) *v*: 3379, 2942, 2868, 1442, 1377, 1295, 1131, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.93 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.69 (t, ^3J (H,H) = 7.6 Hz, 1H), 7.61 (t, ^3J (H,H) = 6.8 Hz, 2H), 4.32 (q, ^3J (H,H) = 7.6 Hz, 1H), 4.27 (t, ^3J (H,H) = 7.6 Hz, 1H), 3.94 (t, ^3J (H,H) = 7.6 Hz, 1H), 3.81 (q, ^3J (H,H) = 7.6 Hz,1H), 3.29 (dt, ^3J (H,H) = 6.9, 7.7 Hz, 1H), 3.10 (dt, ^3J (H,H) = 6.9, 7.7 Hz, 1H), 2.63–2.60 (m, 1H), 2.20–2.10 (m, 1H), 1.98–1.95 (m, 1H), 1.93–1.83 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 140.1, 133.9, 129.3, 127.8, 69.5, 66.8, 65.5, 55.6, 25 ppm; HRMS (EI) $C_{12}H_{15}NO_3S$ requires (M+Na) 276.0665; found 276.0649.

5.3.2. (3*S**,3a*R**)-3-Phenylsulfonyl-hexahydropyrrolo[1,2-*b*]isoxazole 6b

IR (film) *v*: 3436, 2958, 2860, 1442, 1393, 1299, 1144, 1078 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.93 (d, ^3J (H,H) = 7.0 Hz, 2H), 7.70 (t, ^3J (H,H) = 7.5 Hz, 2H), 7.62 (t, ^3J (H,H) = 6.7 Hz, 2H), 4.16–4.11 (m, 2H), 4.05 (ddd, ^3J (H,H) = 4.6, 8.8, 12.7 Hz, 1H), 3.76 (ddd, ^3J (H,H) = 4.6, 7.3, 7.3 Hz, 1H), 3.20 (ddd, ^3J (H,H) = 3.4, 7.9, 13.0 Hz, 1H), 2.99 (dt, ^3J (H,H) = 13.0, 7.9 Hz, 1H), 2.05–1.94 (m, 1H), 1.94–1.86 (m, 1H), 1.78–1.69 (m, 1H), 1.65–1.60 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 137.9, 134.2, 129.5, 128.6, 74.2, 66.2, 55.8, 31, 23.6 ppm; HRMS (EI) $C_{12}H_{15}NO_3S$ requires (M+Na) 276.0665; found 276.0669.

5.3.3. (2*R**,3a*R**)-2-Phenylsulfonyl-hexahydropyrrolo[1,2-*b*]isoxazole 6c

IR (film) *v*: 3436, 3068, 2946, 2868, 1442, 1377, 1307, 1148, 1074 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.99 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.70 (t, ^3J (H,H) = 7.9 Hz, 1H), 7.58 (t, ^3J (H,H) = 8.0 Hz, 2H), 5.04 (dd, ^3J (H,H) = 4.0, 8.4 Hz, 1H), 3.85–3.81 (m, 1H), 3.36–3.31 (m, 1H), 3.23 (ddd, ^3J (H,H) = 4.0, 7.0, 12.4 Hz, 1H), 3.05 (dt, ^3J (H,H) = 8.3, 13.8 Hz, 1H), 2.50 (ddd, ^3J (H,H) = 4.0, 8.4, 12.4 Hz, 1H), 2.04–1.93 (m, 2H), 1.76–1.74 (m, 1H), 1.60–1.57 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 136.7, 133.9, 129.5, 128.9, 92.5, 65.5, 57.3, 36.8, 30.8, 23.8 ppm; HRMS (EI) $C_{12}H_{15}NO_3S$ requires (M+Na) 276.0665; found 276.0682.

5.3.4. (2*S**,3a*R**)-2-Phenylsulfonyl-hexahydropyrrolo[1,2-*b*]isoxazole 6d

IR (film) *v*: 3395, 3056 2942, 2872, 1454, 1332, 1136, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.91 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.66 (t, ^3J (H,H) = 8.0 Hz, 1H), 7.56 (t, ^3J (H,H) = 8.0 Hz, 2H), 4.94 (t, ^3J (H,H) = 8.2 Hz, 1H), 3.80 (m, 1H), 3.46 (dt, ^3J (H,H) = 5.4, 12.7 Hz, 1H), 3.06 (dd, ^3J (H,H) = 7.3, 12.7 Hz, 1H), 2.88 (dt, ^3J (H,H) = 8.2, 13.5 Hz, 1H), 2.73 (ddd, ^3J (H,H) = 7.9, 8.2, 13.5 Hz, 1H), 2.11–2.05 (m, 1H), 1.95–1.92 (m, 1H), 1.89–1.85 (m, 1H), 1.77–1.75 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 137, 134, 129.5, 129, 93.3, 65.5, 56.5, 36.6, 28.3, 23.3 ppm; HRMS (EI) $C_{12}H_{15}NO_3S$ requires (M+Na) 276.0665; found 276.0655.

5.4. Cycloaddition of nitrone 4 to phenyl vinyl sulfone 1

Table 3, entry 2: Phenyl vinyl sulfone **1** (710 mg, 4.23 mmol) was added to a solution of nitrone **4** (1.01 g, 3.38 mmol) in toluene (11.5 mL) at rt. The resulting mixture was stirred for 6 h, then it was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated. The resulting crude residue was purified by flash chromatography (silica gel, hexane/EtOAc 6:4) to obtain isoxazolidines **7a**, **7b**, **7c,** and **7d** in 45% combined yield. Ratio Table 3.

5.4.1. (3*R*,3a*R*,4*S*,5*S*)-4,5-Bis(benzyloxy)-3-phenylsulfonyl-hexahydropyrrolo[1,2-*b*]isoxazole 7a

$[\alpha]_D^{20} = +84.3$ (*c* 0.9, $CHCl_3$); IR (film) *v*: 3064, 3027, 2929, 2856, 1577, 1450, 1307, 1140 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.90 (d, ^3J (H,H) = 8.2 Hz, 2H), 7.69 (t, ^3J (H,H) = 7.6 Hz, 1H), 7.59 (t, ^3J (H,H) = 7.6 Hz, 2H), 7.36–7.22 (m, 10H), 4.53 (d, ^3J (H,H) = 11.6 Hz, 1H), 4.50 (d, ^3J (H,H) = 11.7 Hz, 2H), 4.40 (d, ^3J (H,H) = 11.6 Hz, 1H), 4.21–4.13 (m, 3H), 4.04–3.97 (m, 3H), 3.51 (dd, ^3J (H,H) = 5.2, 14.0 Hz, 1H), 3.19 ppm (dd, ^3J (H,H) = 1.8, 14 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 137.5, 137.3, 137.2, 134.3, 129.5, 128.8, 128.6, 128.5, 128.0, 127.9, 127.7, 86.3, 82.8, 71.7, 71.6, 70.9, 66.3, 59.1 ppm; HRMS (EI) $C_{26}H_{27}NO_5S$ requires (M+Na) 488.1502; found 488.1484.

5.4.2. (3*S*,3a*R*,4*S*,5*S*)-4,5-Bis(benzyloxy)-3-phenylsulfonyl-hexahydropyrrolo[1,2-*b*]isoxazole 7b

$[\alpha]_D^{20} = +58.0$ (*c* 0.3, $CHCl_3$); IR (film) *v*: 3399, 3064, 3027, 2933, 2856, 1462, 1377, 1315, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°,

TMS): δ = 7.94 (d, ^3J (H,H) = 8.0 Hz, 2H), 7.65 (t, ^3J (H,H) = 7.8 Hz, 1H), 7.49 (t, ^3J (H,H) = 7.8 Hz, 2H), 7.37–7.25 (m, 10H), 5.14 (d, ^3J (H,H) = 2.7 Hz, 1H), 4.76 (m, 2H), 4.63 (m, 2H), 4.42 (m, 1H), 4.32 (m, 1H), 4.16 (dd, ^3J (H,H) = 2.7, 5.2 Hz, 1H), 3.95 (m, 1H), 3.86 (t, ^3J (H,H) = 5 Hz, 1H), 3.44–3.36 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 138.9, 137.8, 137.7, 134.1, 129.5, 129.2, 128.9, 128.5, 128.3, 128, 127.8, 84.6, 84.0, 72.7, 71.8, 65.3, 68.3, 59.1 ppm; HRMS (EI) $C_{26}H_{27}NO_5S$ requires (M+Na) 488.1502; found 488.1510.

5.4.3. (2*R*,3a*S*,4*S*,5*S*)-4,5-Bis(benzyloxy)-2-phenylsulfonyl-hexahydropyrrolo[1,2-*b*]isoxazole 7c

$[\alpha]_D^{20} = +90.5$ (*c* 0.2, $CHCl_3$); IR (film) ν: 3412, 3052 3023, 2925, 2860, 1442, 1307, 1066, 1144 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 25°, TMS): δ = 7.96 (d, *J* = 8.1 Hz, 2H), 7.58 (t, ^3J (H,H) = 7.6 Hz, 1H), 7.55 (t, ^3J (H,H) = 7.8 Hz, 2H), 7.34–7.22 (m, 10H), 5.07 (dd, ^3J (H,H) = 3.4, 8.2 Hz, 1H), 4.52 (d, ^3J (H,H) = 11.7 Hz, 2H), 4.48 (d, ^3J (H,H) = 11.7 Hz, 1H), 4.43 (d, ^3J (H,H) = 11.7 Hz, 1H), 4.09 (dd, ^3J (H,H) = 3.0, 5.4 Hz, 1H), 3.95–3.90 (m, 2H), 3.48 (dd, ^3J (H,H) = 5.4, 14.4 Hz, 1H), 3.39 (dd, ^3J (H,H) = 3.0, 14.4 Hz, 1H), 3.21 (ddd, ^3J (H,H) = 3.4, 8.2, 14.0 Hz,, 1H), 2.72 ppm (ddd, ^3J (H,H) = 5.6, 8.2, 14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25°, TMS): δ = 138.5, 137.4, 137.3, 134.0, 129.5, 129.3, 129.0, 128.5, 128.0, 127.9, 127.7, 92.7, 87.9, 84.3, 71.9, 71.6, 69.8, 60.1, 34.9 ppm; HRMS (EI) $C_{26}H_{27}NO_5S$ requires (M+Na) 488.1502; found 488.1482.

5.5. Conversion of 5b into 5a

A stirred solution of isoxazolidine **5b** (34.5 mg, 0.22 mmol) in toluene (0.5 mL) was heated at 110 °C. After 72 h the reaction was quenched with saturated aqueous solution of NH_4Cl and the product was extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated, obtaining isoxazolidine **5a** in a 100% yield.

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