

Site- and regioselectivity of nitrile oxide-allene cycloadditions: DFT-based semiquantitative predictions.

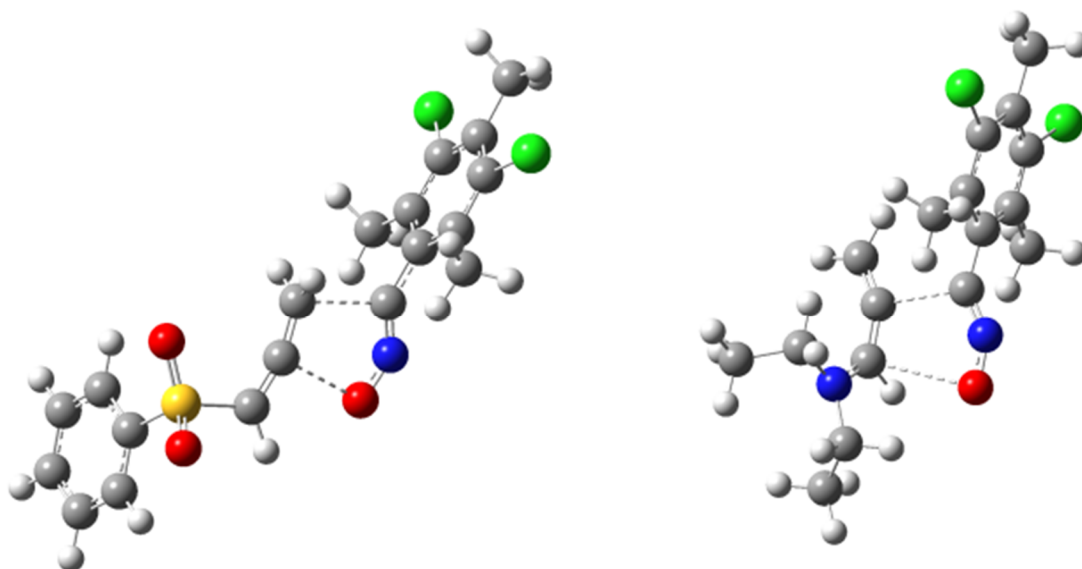
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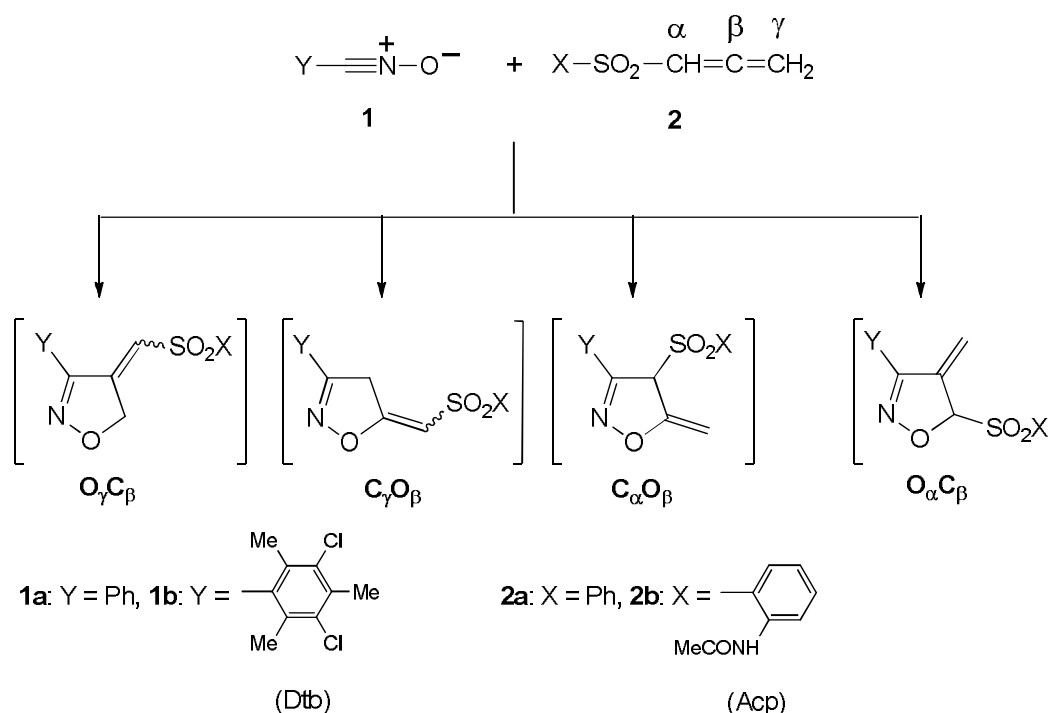
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Abstract - Nitrile oxide 1,3-dipolar cycloaddition to arylsulfonyl- and dialkylamino-allenes have been investigated within the framework of the Kohn-Sham density functional theory

(DFT) at the B3LYP/6-31G(d,p) level. The hitherto unexplained experimental behaviour of sulfonylallenes was rationalised by transition state calculations which enabled a semiquantitative treatment of the cycloaddition site- and regioselectivity. The reliability of DFT computations was further established by predicting the complete selectivity of the nitrile oxide cycloaddition to dialkylaminoallenes, according to previous experimental findings.

Due to the peculiar features of the cumulated 1,2-diene system, allenes have attracted the interest of organic chemists since long time ago.¹⁻³ As a result, allenes have been submitted to a number of useful synthetic transformations,⁴⁻⁷ including 1,3-dipolar cycloadditions.^{8,9} The low reactivity of the allene moiety as dipolarophile¹⁰ can be circumvented by the presence of appropriate activating substituents. However, it may be pointed out that intermolecular 1,3-dipolar cycloadditions to monosubstituted allenes can display different site-, regio- and stereoselectivities since both allene double bonds are suitable sites for dipolar attack. As an example, the intermolecular cycloadditions between monosubstituted allenes and nitrile imines give rise to mixtures of products arising from competitive site- and regiochemical course.^{11,12} Focussing on the intermolecular cycloadditions between nitrile oxides and monosubstituted allenes, a quite different behaviour is observed according to the electronic nature of the allene substituent.⁹ Cycloadditions of nitrile oxides **1** to sulfonylallenes **2**¹³⁻¹⁵ and aminoallenes **3**¹⁶⁻¹⁸ have been studied in detail giving a complementary site-selectivity (Scheme 1 and 2, Table 1). The only cycloaddition pathway involved in the case of aminoallenes **3** relies upon the primary cycloadduct **O_αC_β-II** which can usually be isolated and characterised, *i.e.* only the α,β -double bond of the allene moiety is involved in the cycloaddition. By contrast, sulfonylallenes **2** always give mixtures of isomeric isoxazoles since all the four primary cycloadducts are formed as unstable intermediates due to the participation of both allene α,β - and β,γ -double bonds. Although mechanistic evidences points to the poor site- and regioselective behaviour of sulfonylallenes, there was quite a debate on this point.^{14,15}

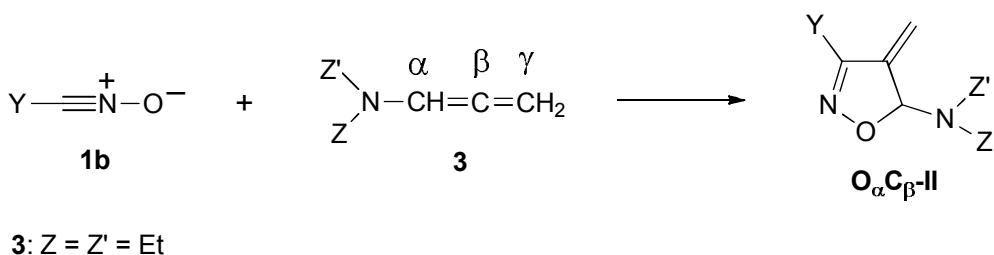


Scheme 1. Primary cycloadducts generated in the reaction between nitrile oxides **1** and arylsulfonylallenes **2**.

Table 1. Primary cycloadducts generated in the reaction between nitrile oxides **1** and arylsulfonylallenes **2**.

Entry	Y	X	1 : 2 ratio	Intermediates (%) ^a				β,γ : α,β ratio	Ref.
				O _γ C _β	C _γ O _β	C _α O _β	O _α C _β		
1	Ph	Ph	1 : 1	0	52	6	4	84 : 16	15
2	Dtb	Ph	1 : 1	23	23	2.5	4	88 : 12	13
3	Dtb	Ph	2.5 : 1	22	36	14	1	67 : 33	13
4	Dtb	Acp	1 : 1	26	22	14	10	67 : 33	14
5	Dtb	Acp	2 : 1	26	29	11	8	74 : 26	14
6	Dtb	Acp	4 : 1	24	37	9	8	78 : 22	14

^a Deduced from experimental product yields and mechanistic findings of the corresponding paper (Ref.).



Scheme 2. Cycloadduct generated in the reaction between nitrile oxide **1b** and aminoallene **3**.

Theoretical efforts have been pursued in order to rationalise the nitrile oxide-allene behaviour within the frame of FMO theory.¹⁹ Although the nitrile oxide reaction to aminoallenes was tentatively predicted to be a simple α,β -cycloaddition,¹⁶ it should be highlighted that the FMO model is not suitable in the case of sulfonylallenes. In fact, early CNDO calculations show that the frontier orbital features of 1-(methylsulfonyl)-1,2-propadiene would allow selective nitrile oxide attack to the α,β -double bond.²⁰ To accommodate this incongruity, it was proposed a reaction pathway involving a site-selective cycloaddition across the α,β -double bond and subsequent 1,3-shift of the arylsulfonyl group, thus simulating a β,γ -cycloaddition; in this case only the two primary cycloadducts $C_\alpha O_\beta$ and $O_\alpha C_\beta$ would be formed.¹⁵ This picture has been challenged since it was proved that the 1,3-arylsulfonyl shift cannot occur and all the four primary adducts are formed.¹⁴ We were thus prompted to computationally investigate these cycloadditions. A widespread approach is based on the analysis of density functional theory (DFT) reactivity indices,²¹ which was successfully applied to the cycloaddition of nitrile oxides.^{22,23} However, this method only takes purely electronic factors into account but neglects thermal and steric factors that can be important in medium-sized, crowded TSs. Therefore, in the present paper the cycloaddition between nitrile oxides **1** and allenes **2** and **3** was investigated within the frame of density functional theory (DFT) providing reliable semiquantitative predictions which agree with the non-selective mechanistic picture.

The four possible transition states (TSs) leading to the corresponding intermediates $C_\gamma O_\beta$, $O_\gamma C_\beta$, $C_\alpha O_\beta$ and $O_\alpha C_\beta$ for the investigated **1** + **2** and **1b** + **3** cycloadditions were calculated within the framework of Kohn-Sham DFT using the B3LYP functional. We started by investigating the reaction between benzonitrile oxide **1a** and phenylsulfonylallene **2a** (X = Ph, Y = Ph) using three basis sets of increasing size: polarized double- ζ 6-31G(d,p), polarized triple- ζ 6-311G(d,p), and augmented polarized triple- ζ 6-311+G(d,p). The main

computational results are collected in Table 2 and Figure 1 (see Supporting Information for TS molecular structures). Temperature-dependent contributions to ΔG were computed at the boiling point of CCl_4 (350.15 K) since the investigated reactions were carried out in refluxing CCl_4 (See references in Table 1).

Table 2. Relative electronic energy ΔE and Gibbs free energy ΔG at $T = 350.15$ K of the four transition states for the **1a** + **2a** cycloaddition calculated using the B3LYP functional and the 6-31G(d,p), 6-311G(d,p), and 6-311+G(d,p) basis sets. ΔE and ΔG are calculated as difference from the most stable transition state.

	ΔE (kcal mol ⁻¹)			ΔG (kcal mol ⁻¹)		
	6-31G(d,p)	6-311G(d,p)	6-311+G(d,p)	6-31G(d,p)	6-311G(d,p)	6-311+G(d,p)
$\text{O}_\gamma\text{C}_\beta$	0.88	0.83	0.56	1.45	0.67	2.55
$\text{C}_\gamma\text{O}_\beta$	0.00	0.00	0.00	0.00	0.00	0.00
$\text{C}_\alpha\text{O}_\beta$	0.40	0.31	0.66	2.19	1.95	1.79
$\text{O}_\alpha\text{C}_\beta$	3.47	3.19	3.59	4.33	3.79	3.79

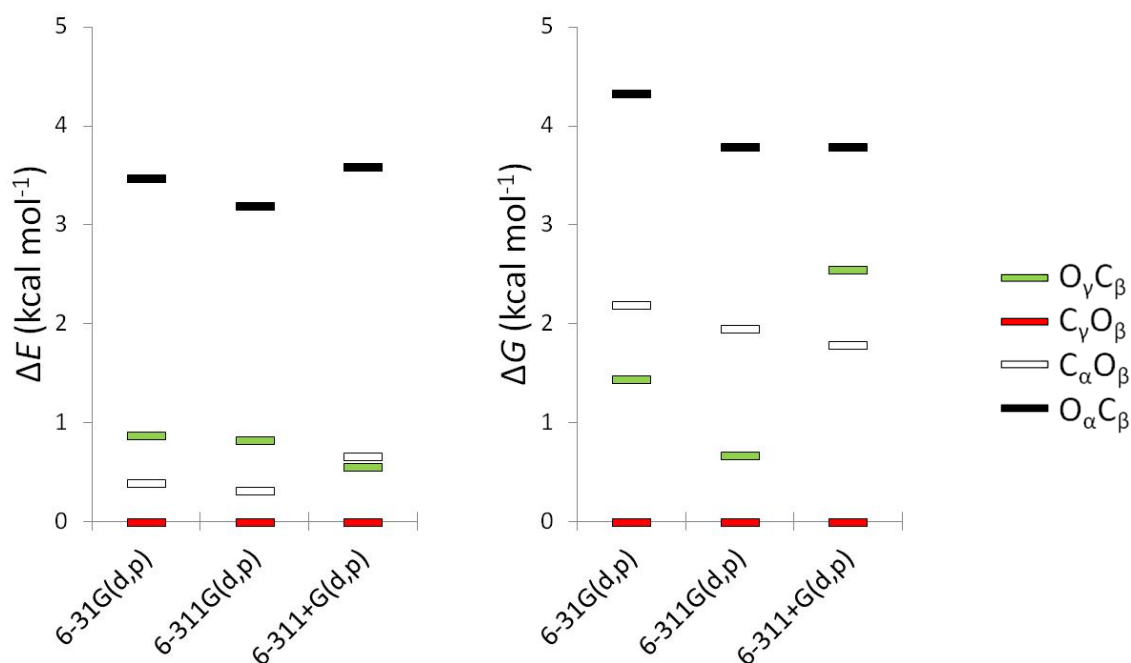


Figure 1. Relative electronic energy ΔE and Gibbs free energy ΔG at $T = 350.15$ K of the four transition states for the **1a** + **2a** cycloaddition calculated using the B3LYP functional and the 6-31G(d,p), 6-311G(d,p), and 6-311+G(d,p) basis sets. ΔE and ΔG are calculated as difference from the most stable transition state.

Clearly, all basis sets gave similar results. The $\mathbf{C}_\gamma\mathbf{O}_\beta$ TS has lowest energy in all cases. The energy order of the TSs is independent of the basis set except for the $\Delta G(350.15\text{ K})$ of the $\mathbf{O}_\gamma\mathbf{C}_\beta$ TS when the augmented basis set is used. The maximum differences from the 6-31G(d,p) results are $0.32\text{ kcal mol}^{-1}$ in ΔE and $1.10\text{ kcal mol}^{-1}$ in ΔG . Furthermore, the lengths of the newly forming O-C and C-C bonds and the $\text{C}\equiv\text{N}-\text{O}$ and $\text{CH}=\text{C}=\text{CH}_2$ angles are also very similar (see Supporting Information). We thus conclude that the 6-31G(d,p) basis set is suitable for our purposes.

To complete the investigation of the reactions involving sulfonylallenes, we next calculated the four TSs for the cycloaddition of 3,5-dichloro-2,4,6-trimethyl-benzonitrile oxide **1b** ($Y = \text{Dtb}$) to phenylsulfonylallene **2a** ($X = \text{Ph}$) and 2-acetylammino-phenylsulfonylallene **2b** ($X = \text{Acp}$) at the B3LYP/6-31G(d,p) level. The main computational results are collected in Table 3 and Figure 2, while selected TSs are shown in Figure 3.

Table 3. Relative electronic energy ΔE and Gibbs free energy ΔG at $T = 350.15\text{ K}$ of the four TSs for the nitrile oxide - allene cycloadditions calculated using the B3LYP functional and the 6-31G(d,p) basis set. ΔE and ΔG are calculated as difference from the most stable transition state.

	ΔE (kcal mol $^{-1}$)				ΔG (kcal mol $^{-1}$)			
	1a+2a	1b+2a	1b+2b	1b+3	1a+2a	1b+2a	1b+2b	1b+3
$\mathbf{O}_\gamma\mathbf{C}_\beta$	0.88	0.18	0.00	4.58	1.45	0.11	0.28	6.20
$\mathbf{C}_\gamma\mathbf{O}_\beta$	0.00	0.30	1.85	5.16	0.00	0.00	0.00	5.85
$\mathbf{C}_\alpha\mathbf{O}_\beta$	0.40	0.00	1.22	10.70	2.19	1.38	0.45	11.43
$\mathbf{O}_\alpha\mathbf{C}_\beta$	3.47	1.53	9.23	0.00	4.33	3.28	8.12	0.00

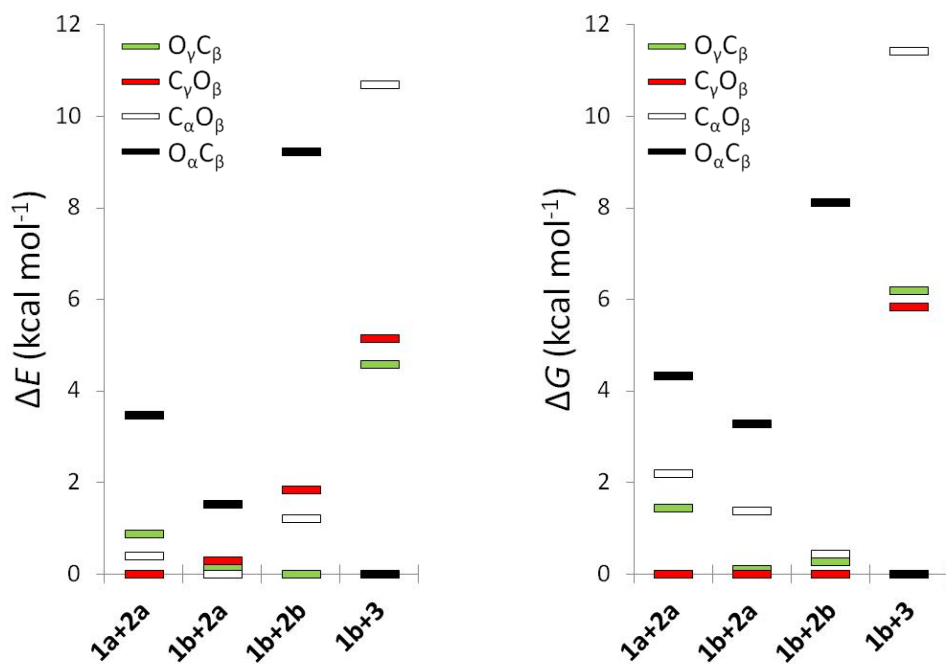
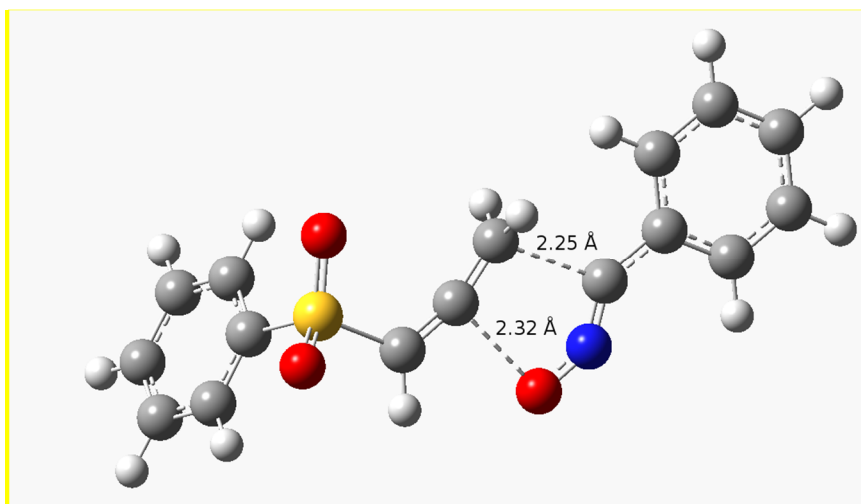


Figure 2. Relative electronic energy ΔE (left) and Gibbs free energy ΔG at $T = 350.15$ K (right) of the four TSs for the nitrile oxide - allene cycloadditions calculated using the B3LYP functional and the 6-31G(d,p) basis set. ΔE and ΔG are calculated as difference from the most stable transition state.

a)



b)

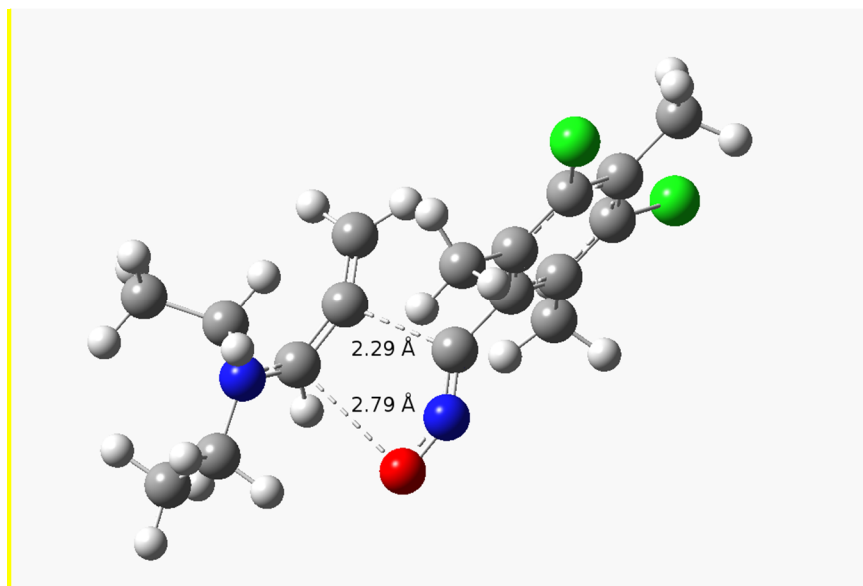


Figure 3. Lowest-energy transition states for the **1a+2a** (a, $C_\gamma O_\beta$) and **1b+3** (b, $O_\alpha C_\beta$) nitrile oxide - allene cycloadditions calculated using the B3LYP functional and the 6-31G(d,p) basis set. Color code: hydrogen: white, carbon: gray, nitrogen: blue, oxygen: red, sulfur: yellow, chlorine: green.

Considering ΔE , we can see that the most stable TS is a different one in each **1 + 2** reaction, the $C_\gamma O_\beta$ TS for **1a+2a**, $C_\alpha O_\beta$ TS for **1b+2a**, and $O_\gamma C_\beta$ TS for **1b+2b**. However, these isomeric TSs have similar ΔE , sometimes differing by less than 1 kcal mol⁻¹. The $O_\alpha C_\beta$ TS is clearly disfavoured in each reaction. The enthalpy difference ΔH is strictly proportional to ΔE and thus not worth considering. The calculated Gibbs energy includes entropic effects arising from temperature-dependent population of vibrational states. When ΔG is considered, the relative stability of the TSs is clearer: for all **1 + 2** reactions the $C_\gamma O_\beta$ TS is the most favoured, followed by $O_\gamma C_\beta$ and $C_\alpha O_\beta$ TSs, leaving the $O_\alpha C_\beta$ TS as the least favoured one. To support the reliability of the present computational approach, we also investigated the four TSs of the **1b + 3** cycloaddition: in this case, the $O_\alpha C_\beta$ TS is the most stable one by 5-6 kcal mol⁻¹ for both ΔE and ΔG .

We now compare the structure of the TSs leading to the *same* regioisomer among the three reactions involving sulfonyl allenes **2**. It turns out that their geometry is very similar. The length of the forming bonds differ by less than 0.07 Å, while the $C\equiv N-O$ and $CH=C=CH_2$ angles differ by less than 3 degree (see Supporting Information). Given this similarity, one wonders if the relative stability of the TSs leading to *different* regioisomeric products of the **1 + 2** cycloaddition is related to the molecular geometry. The most stable

$C_\gamma O_\beta$ TS has the largest $CH=C=CH_2$ angle (162°), while the least stable $O_\alpha C_\beta$ TS has the lowest angle (151°); $O_\gamma C_\beta$ and $C_\alpha O_\beta$ TSs display intermediate values (153° and 156° , respectively). The $C\equiv N-O$ angle is almost constant at $(141 \pm 1)^\circ$. This suggests that the TS stability is related to the distortion of the allenic moiety. Significant differences are also observed for the lengths of the new-forming bonds. In the $O_\gamma C_\beta$, $C_\gamma O_\beta$, and $O_\alpha C_\beta$ TSs, the lengths are very similar, encompassing the range 2.25-2.30 Å, whereas in the $C_\alpha O_\beta$ TS the $O-C_\beta$ bond is shorter (2.05 Å) than the $C-C_\alpha$ one (2.40 Å). Such difference might be responsible for the high energy of the $C_\alpha O_\beta$ TS. Considering now the geometry of the four TSs of the **1b** + **3** reaction, one finds that when the nitrile oxide oxygen binds to the allene β -carbon ($C_\gamma O_\beta$ and $C_\alpha O_\beta$) the TSs have geometry very similar to those of the **1** + **2** cycloadditions, whereas the $O_\gamma C_\beta$ and $O_\alpha C_\beta$ TSs have longer $O\cdots C$ bonds (2.53 and 2.79 Å, respectively) and less symmetric TSs. In this case, the most stable TS has the largest $C\equiv N-O$ angle (146°) and the smallest $CH=C=CH_2$ angle (146°). A general relationship between TS structure and energy thus seems not to exist.

Assuming that the reactions leading to the primary cycloadducts are under kinetic control and that no other reaction appreciably occurs, the fraction p of each regioisomeric product can be calculated as

$$p_i = \frac{\exp(-\Delta G_i/RT)}{\sum_i \exp(-\Delta G_i/RT)}$$

The calculated regio- and site-selectivities are collected in Table 4. Semi-quantitative agreement of the calculated site- and regioselectivity with the experimental data is readily apparent. Attack to the β,γ double bond of the sulfonyl allenes **2** is favoured in all reactions and substantial amounts of both $O_\gamma C_\beta$ and $C_\gamma O_\beta$ regioisomers are expected. The site-selectivity of the **1b** + **2b** cycloaddition is lower due to the formation of some $C_\alpha O_\beta$ isomer. The latter is the only isomer formed on attack to the allenic α,β -double bond. Replacement of $Y = Ph$ with $Y = Dtb$ does not significantly affect the site-selectivity but it causes a large regioselectivity change among the two β,γ regioisomers whereas the $X = Acp$ substituent causes a lower site-selectivity but has scarce effect on the regioselectivity, in comparison to the $X = Ph$ case. The **1b** + **3** cycloaddition has complete site- and regioselectivity since calculation predicts that only the $O_\alpha C_\beta$ -II cycloadduct forms at 350 K.

Table 4. Regio- and siteselectivity for the nitrile oxide - allene cycloadditions calculated using the B3LYP functional and the 6-31G(d,p) basis set.

	Y	X / Z ^a	Intermediates (%)				β,γ : α,β ratio
			$O_\gamma C_\beta$	$C_\gamma O_\beta$	$C_\alpha O_\beta$	$O_\alpha C_\beta$	
1a + 2a	Ph	Ph	11	85	4	0	96 : 4
1b + 2a	Dtb	Ph	43	50	7	0	93 : 7
1b + 2b	Dtb	Acp	31	46	24	0	76 : 24
1b + 3	Dtb	Et	0	0	0	100	0 : 100

^a X is related to compounds **2a** and **2b**, Z (= Z') is related to compound **3**.

Using DFT to compute the relative TS energy allowed us to naturally introduce the inductive, conjugative and hyperconjugative effects of the sulfonyl group, which caused interpretation difficulties,²⁴⁻²⁶ and to take entropic effects into consideration. As can be seen, the site- and regioselectivity calculated for the nitrile oxide-sulfonylallene cycloadditions are fully consistent to the experimental findings outlined in the Table 1. This suggests that both electronic and entropic effects are important for the relative stability of the TSs. The agreement between experimental and computational results is worth of noting since the experimental outcome of such reactions is somewhat complex and not predictable by means of the FMO properties of sulfonylallenes.²⁰ The reliability of the present computations is further substantiated by the prediction that only the α,β -double bond of aminoallene **3** is involved in the reaction with nitrile oxides, thus providing a firm theoretical background in the field of nitrile oxide-allene cycloadditions.

Computational Methods

DFT calculations were performed with the Gaussian09 program suite.²⁷ The B3LYP functional was employed with the standard 6-31G(d,p), 6-311G(d,p), and 6-311+G(d,p) basis sets. The geometry of all TSs was fully optimized and characterized by harmonic analysis at the reaction temperature $T = 350.15$ K (77 °C). All transition states have a single imaginary frequency.

Supporting Information. Energy and geometric parameters of the transition states of the **1a** + **2a** cycloaddition calculated with the 6-31G(d,p), 6-311G(d,p), and 6-311+G(d,p) basis set; energy and geometric parameters of the transition states of all cycloadditions; optimized molecular structures of the four TSs of the **1a** + **2a** cycloaddition; Cartesian coordinates, number of imaginary frequencies, and computed total energies of all located transition states.

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