

A Theoretical Rationalization of the Asymmetric Induction in Sulfinyl-Directed [5C + 2C] Intramolecular Cycloadditions

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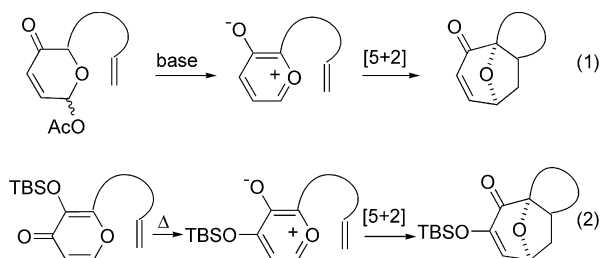
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A computational DFT examination (B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G*) of the thermal [5C + 2C] cycloadditions of 6-acetoxy-3-pyranones and 3-silyloxy-4-pyrones with tethered alkenyl sulfoxides confirms that the high level of diastereofacial selectivity obtained is ultimately due to the preference of the alkenesulfinyl group to adopt a well-defined conformation in the transition state of the reaction. This conformation, which is different from that found in the ground state, is most probably dictated by dipolar interaction effects between the sulfoxide and the oxidopyrylium ylide intermediate.

Introduction

It is well-known that treatment of 6-acetoxy-3-pyranones with an appropriate base generates 3-oxidopyrylium ylides and that these intermediates can participate as five-carbon partners in a variety of [5C + 2C] cycloadditions with activated alkenes or alkynes.¹ The intramolecular version of this reaction is particularly useful as it allows relatively complex oxa-bridged bicyclic products to be constructed from simple precursors in a practical and rapid manner (Scheme 1, eq 1).² On the other hand, it has also been shown that related products containing a higher oxygenated cycloheptane ring can be prepared by means of a thermally induced intramolecular cycloaddition between β -silyloxy- γ -pyrones and alkenes.³ This cycloaddition also proceeds through the intermediacy of a 3-oxidopyrylium dipole, in this case bearing an additional 4-silyloxy substituent (Scheme 1, eq 2).⁴ The skeletal, functional, and stereochemical richness of the resulting cycloadducts has allowed a variety of divergent manipulations to be performed, leading to different types of synthetically valuable products.⁵

SCHEME 1



Given the synthetic potential of the adducts, the development of asymmetric versions of the above cycloadditions that could lead to enantiomerically pure products is of major interest.⁶ In this context, we have recently shown that the introduction of a homochiral *p*-tolylsulfinyl group at an appropriate position of the alkene provides excellent levels of diastereofacial selection in both types of cycloaddition. For example, the addition of DBU to 6-acetoxy-3-pyranone **1a** leads to the formation of an oxidopyrylium ylide intermediate that undergoes an intramolecular cycloaddition to give oxabicyclic **2** in good yield.⁷ The reaction proceeds even at -30 °C, and the diastereoisomeric ratios varied from 85:15, when the reaction was carried out in acetonitrile or DMF, to 100:0 when a less polar solvent like toluene was employed (Table 1).

On the other hand, the intramolecular cycloaddition of β -silyloxy- γ -pyrones **3a–c**, which can be promoted by simple reflux in toluene, also gave the expected [5C + 2C] cycloadducts with high levels of diastereoselectivity

* Corresponding author.

(1) (a) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359. (b) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1261.

(2) (a) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1057. (b) Bromidge, S. M.; Sammes, P. G.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1725. (c) Wender, P. A.; Rice, K. D.; Schnute, M. E. *J. Am. Chem. Soc.* **1997**, *119*, 7897. (d) Wender, P. A.; Jesudason, C. D.; Nakahira, H.; Tamura, N.; Tebbe, A. L.; Ueno, Y. *J. Am. Chem. Soc.* **1997**, *119*, 12976.


(3) (a) Mascareñas, J. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford, 1999; Vol. 6, pp 1–54. (b) Rumbo, A.; Castedo, L.; Mouriño, A.; Mascareñas, J. L. *J. Org. Chem.* **1993**, *58*, 5585.

(4) Domingo, L. R.; Zaragoza, R. J. *J. Org. Chem.* **2000**, *65*, 5480.

(5) (a) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Synthesis* **2000**, 7, 980. (b) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **2000**, *65*, 2528. (c) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 4560. (d) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 966.

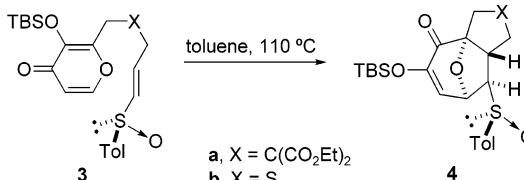
(6) (a) Hodgson, D. M.; Labande, A. H.; Pierard, F. Y. T. M. *Synlett* **2003**, 59. (b) Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465 and references therein. (c) Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 5811. (d) Rumbo, A.; Castedo, L.; Mascareñas, J. L. *Tetrahedron Lett.* **1997**, *38*, 5885. (e) Ohmori, N.; Yoshimura, M.; Ohkata, K. *Heterocycles* **1997**, *45*, 2097.

(7) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2002**, *4*, 3683.

TABLE 1. Intramolecular Cycloaddition of 1a


solvent	T (°C)	dr ^b	time (min)	yield ^c (%)
CH ₃ CN	20	85:15	5	77
CH ₃ CN	-30	88:12	90	82
CH ₂ Cl ₂	-30	100:0 ^a	150	78
toluene	-30	100:0 ^a	180	86
toluene	0	100:0 ^a	60	81
Et ₂ O	-30	96:4	180	80

^a Minor diastereoisomer not detected by NMR. ^b Diastereoisomeric ratio. ^c Combined isolated yield.

TABLE 2. Intramolecular Cycloaddition of 3


substrate	dr	time (h)	yield ^a (%)
3a	97:3	3.5	99
3b	93:7	46	95
3c	91:9	10	98

a, X = C(CO₂Et)₂
 b, X = S
 c, X = C(CN)₂

^a Combined isolated yield.

(Table 2).⁸ Interestingly, whereas the reaction of **3a** is complete after only 3.5 h, the cycloaddition of an homologue substrate bearing a hydrogen atom in place of the *p*-tolylsulfinyl group requires heating for more than 12 h for completion. This observation suggests that the presence of the sulfinyl group significantly accelerates the cycloaddition process.

In an effort to explain the stereochemical course of the above cycloadditions, we have proposed a qualitative model in which it is assumed that the alkenyl sulfoxide unit prefers to adopt an *s-trans* conformation in the transition state of the reaction and the subsequent approach to the oxidopyrylium ylide would then occur at its less hindered face, which is that containing the sulfur lone pair. To confirm this hypothesis and to obtain more detailed information on the factors that govern the reactivity and diastereoselectivity in the cycloadditions, we have now performed computational calculations to characterize the energy profile and the relevant stationary points in the processes.

Computational Methods

Calculations were performed with the GAUSSIAN 98 suite of programs.⁹ All starting geometries for the DFT calculations were first preoptimized at the semiempirical PM3 level. A value of 2.00 Å was used as the starting measurement for each

(8) (a) López, F.; Castedo, L.; Mascareñas, J. L. *Chem Eur. J.* **2002**, *8*, 884. (b) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2000**, *2*, 1005.

of the newly formed C–C bonds in the transition structures. Previous theoretical studies by other groups on related cycloaddition processes have shown the validity of DFT methods for obtaining accurate data.^{4,10} Given this knowledge, the stationary points were optimized using Becke's three-parameter hybrid functional,¹¹ together with the correlation functional of Lee, Yang, and Parr¹² as implemented in Gaussian 98. Standardized 6-31G* and 6-311+G** basis sets including polarization and diffuse functions were used. Stationary points were located at the B3LYP/6-31G* level. On these geometries single-point calculations at B3LYP/6-311+G** were done. The computed values of activation enthalpies, entropies, and Gibbs energies were estimated by means of the B3LYP/6-31G* potential energy barriers along with the harmonic frequencies. The nature of the stationary points was determined by calculation of harmonic frequencies, which were scaled by 0.96,¹³ to identify minima (zero imaginary frequencies) and transition structures (one imaginary frequencies) and to obtain zero point vibrational energies and thermal contributions. Solvents effects were taken into account at the B3LYP/6-31G* level using a polarized continuum model (PCM) developed by Tomasi's group included in Gaussian 98.¹⁴

Results and Discussion

Acetoxypyranone/Alkene Cycloaddition. To reduce the computational cost of the calculations, the study was carried out on the simplified model **1b** in which the *p*-tolyl group on the sulfur atom of **1a** was replaced by a phenyl group and the geminal diethyl esters by hydrogens (Scheme 2).¹⁵

Before starting the analysis of the reaction pathway it was considered important to know the intrinsic conformational preferences of a simple alkenyl phenyl sulfoxide as well as the rotational barriers for the interconversion between conformers. Previous ab initio studies by Tietze and co-workers on methyl (*E*)-prop-1-enyl sulfoxide showed that there are two preferred conformations: one with the S–O bond synplanar to the double bond and the other with the lone pair in plane; the first conformer is preferred by 1.2 kcal·mol⁻¹.¹⁶ Our own exploration of the B3LYP/6-31G* potential energy surface (PES) of phenyl (*E*)-prop-1-enyl sulfoxide (**8**) gave results that agree with those reported by Tietze for the methyl

(9) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; González, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.

(10) Diels–Alder reactions: (a) Avalos, M.; Babiano, R.; Clemente, F. R.; Cintas, P.; Gordillo, R.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **2000**, *65*, 8251. (b) García Ruano, J. L.; Clemente, F. R.; González Gutiérrez, L.; Gordillo, R.; Martín Castro, A. M.; Rodríguez Ramos, J. H. *J. Org. Chem.* **2002**, *67*, 2926. 1,3 Dipolar cycloaddition: (c) Domingo, L. R. *J. Org. Chem.* **1999**, *64*, 3922.

(11) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372.

(12) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(13) (a) Scott, A. P.; Radom, L. *J. Phys. Chem.* **1996**, *100*, 16502. (b) Hehre, W.; Radom, L.; Schleyer, P. v. R.; Pople, J. A. *Ab Initio Molecular Orbital Theory*; Wiley: New York, 1986.

(14) Tomasi, J.; Persico, M. *Chem. Rev.* **1994**, *94*, 2027.

(15) Preliminary results of these calculations are included in ref 7.

(16) Tietze, L. F.; Schuffenhauer, A.; Schreiner, P. R. *J. Am. Chem. Soc.* **1998**, *120*, 7952.

SCHEME 2

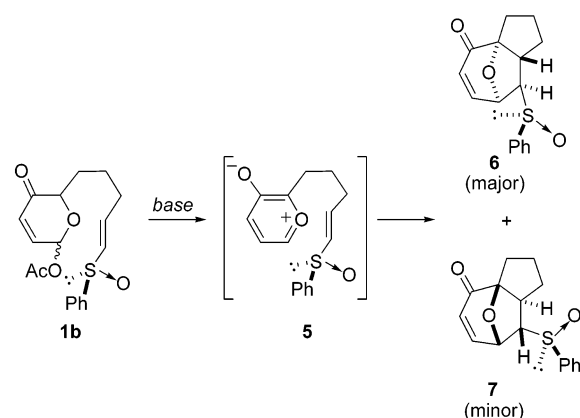


TABLE 3. Conformers Found in the Rotational PES of **8 at Different Levels of Theory**

		8a	8b	8c	8d
B3LYP/6-31G*	E^a	0	0.8	3.4	4.5
	C=C–S=O (deg)	10	127	68	–60
B3LYP/6-311+G**// B3LYP/6-31G*	E^a	0	0.5	3.1	4.1

^a Relative energy (kcal·mol^{–1}).

analogue and show that conformation **8a**, with a C=C–S=O dihedral angle close to 0° (commonly known as *s-cis*), represents the global minimum on the rotational PES. Moreover, a local minimum **8b**, with a C=C–S=O dihedral angle of 127° and a syn coplanarity between the sulfur lone pair and the double bond (commonly denoted as *s-trans*), was located at a point 0.81 kcal·mol^{–1} higher in energy than **8a**. Finally, two maxima in the rotational PES were found for the structures **8c** and **8d**, which correspond to C=C–S=O dihedral angles of 68° and –60°, respectively. The rotational barrier between the most stable conformations **8a** and **8b** is 3.4 kcal·mol^{–1}.

To obtain more precise data, the energy of each of these optimized geometries was recalculated at B3LYP/6-311+G** (Table 3). It can be seen that the results are quite similar and only a slight decrease in the energy differences between the four different conformers is observed. It therefore appears that both levels of theory are suitable to describe the conformational preferences of the alkenyl sulfoxide (Figure 1).

Once the inherent conformational preferences of the dienophile had been established, we optimized the structure of the oxidopyrylium ylide intermediate **5** at the B3LYP/6-31G* level and characterized the two conformers of minimal energy. In this case the calculations showed an energy difference of 1.7 kcal·mol^{–1} between the *s-cis* (C=C–S–O = 8.5°) and the *s-trans* (C=C–S–O = 113°) conformers. This energy gap increased to 2.1 kcal·mol^{–1} when the calculations were carried out at the B3LYP/6-311+G**//B3LYP/6-31G* level.

Computational analysis of the intramolecular cycloaddition of the oxidopyrylium intermediate **5** located four relevant transition states (**TS1**–**TS4**, Table 4). The potential energy profile and the geometries of the TSs are depicted in Figures 2 and 3, respectively.

The lowest energy barrier corresponds to the structure **TS1**, in which the alkenyl sulfoxide adopts an *s-trans* conformation (C=C–S=O = –151°) and approaches the

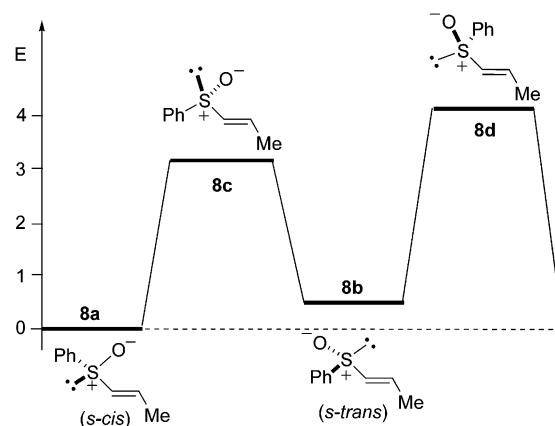


FIGURE 1. Rotational PES of **8** at B3LYP/6-311+G**//B3LYP/6-31G*.

TABLE 4. Relative Energies (kcal·mol^{–1}) for the Stationary Points of the Asymmetric [5 + 2] Cycloaddition of the Oxidopyrylium Ylide **5**

	B3LYP/6-31G*	B3LYP/6-311+G**//B3LYP/6-31G*
5-<i>s-cis</i>	0	0
5-<i>s-trans</i>	1.7	2.1
TS1	10.8 (0) ^a	12.5 (0) ^a
TS2	14.2 (3.4) ^a	15.9 (3.4) ^a
TS3	13.8 (3.0) ^a	16.0 (3.5) ^a
TS4	15.1 (4.3) ^a	17.3 (4.8) ^a
6	–28.5	–25.4
7	–28.1	–24.4

^a Relative to **TS1**.

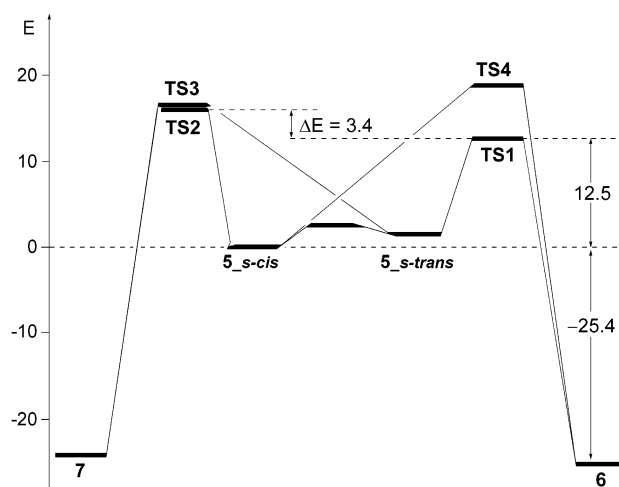


FIGURE 2. Potential energy profile for the cycloaddition of **5** (B3LYP/6-311+G**//B3LYP/6-31G*).

oxidopyrylium ylide from its less hindered face, i.e., opposite to the phenyl group. Two structures are located in the range 3.0–3.5 kcal·mol^{–1} higher in energy: **TS2**, in which the alkenyl sulfoxide is in an *s-cis* conformation (C=C–S=O = –15°) and approaches the oxidopyrylium from its less hindered face, and **TS3**, which is *s-trans* but the approach is from the more congested side of the sulfoxide, i.e., that containing the phenyl ring. Whereas the first structure (**TS1**) leads to the major isomer **6**, both transition states **TS2** and **TS3** would yield the minor diastereoisomer **7**.

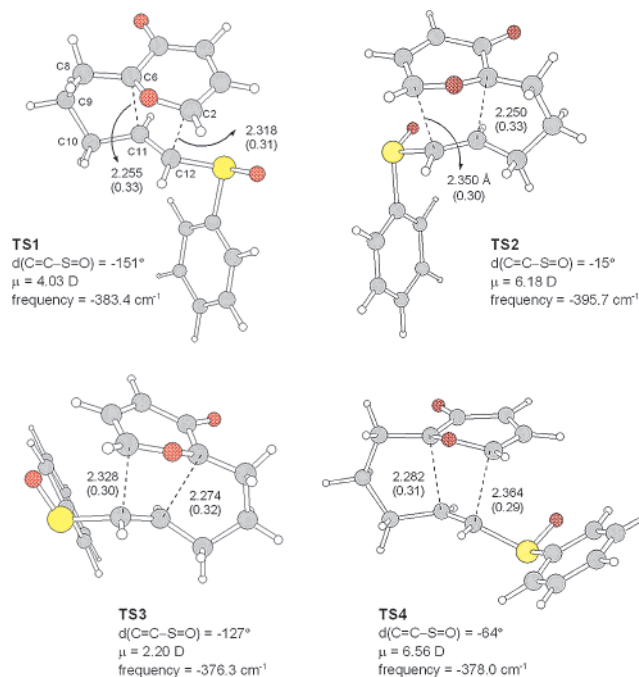


FIGURE 3. B3LYP/6-31G*-optimized geometries, dipolar moments (D), C=C-S=O dihedral angles (deg), and imaginary frequencies (cm^{-1}) for the transition structures **TS1**–**TS4**. The lengths of the C–C bonds involved in the reaction are given in angstroms. Wiberg indices shown in parentheses.

Interestingly, although steric factors might suggest that **TS2** should be less energetic than **TS3**, both TSs are very close in energy. Indeed, **TS3** is $0.3 \text{ kcal}\cdot\text{mol}^{-1}$ more stable than **TS2** at B3LYP/6-31G* and only slightly higher in energy ($0.1 \text{ kcal}\cdot\text{mol}^{-1}$) than **TS2** when the more rigorous B3LYP/6-311+G**//B3LYP/6-31G* level is used. This situation can be explained by considering the existence of dipolar interactions between the sulfinyl and the oxidopyrylium dipoles. These interactions, in line with the calculated dipolar moments of the structures (**TS3**: $\mu = 2.2 \text{ D}$; **TS2** $\mu = 6.2 \text{ D}$), should lead to an increase in the energy of the system when the alkenyl sulfoxide group is in an *s-cis* conformation. Dipolar and steric effects appear to counterbalance and therefore both transition states are of similar energy.

The highest energetic **TS4**, in which the alkenyl sulfoxide approaches the pyrylium in an *s-cis* conformation from the most hindered face, is disfavored by both steric and dipolar grounds (Figure 3).

The observation of similar lengths for the two σ -bonds being formed in the cycloaddition for all the TSs is consistent with a concerted processes in which the two bonds are created symmetrically. The synchronicity of this type of pericyclic reaction is further confirmed by analyzing the bond order (BO) of the TSs, given as the Wiberg indices,¹⁷ and derived from the natural atomic orbital basis. The values obtained are very similar for the two σ -bonds in the four transition states, with the BO of the C6–C11 bond being slightly larger (by only 0.02). On the other hand, the atomic charges corresponding to this intramolecular process were also computed by natural population analysis and were shared by

TABLE 5. Activation Enthalpies ($\text{kcal}\cdot\text{mol}^{-1}$), Entropies ($\text{cal}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$), and Gibbs Energies ($\text{kcal}\cdot\text{mol}^{-1}$) for the Intramolecular Cycloaddition of **5** (B3LYP/6-31G*)^a

	ΔH^\ddagger	ΔS^\ddagger	ΔG^\ddagger
5-s-cis → (TS1) → 6	10.0	–15.5	14.6
5-s-cis → (TS2) → 7	13.3	–14.6	17.7
5-s-cis → (TS3) → 7	13.2	–17.6	18.5
5-s-cis → (TS4) → 6	14.3	–15.6	19.1

^a The activation Gibbs energies were computed at 25 °C.

TABLE 6. Relative Electronic Energies ($\text{kcal}\cdot\text{mol}^{-1}$) and Dipole Moments (Debye Units) of the Four TSs Calculated at B3LYP/6-31G* in the Gas Phase, Toluene, and Acetonitrile

	gas phase		toluene		acetonitrile	
	μ	E^a	μ	E^a	μ	E^a
TS1	4.04	0	4.56	0	5.21	0
TS2	6.18	3.4	7.03	2.8	8.28	1.9
TS3	2.20	3.0	2.50	2.9	3.01	2.6
TS4	6.56	4.3	7.41	3.9	8.53	3.2

^a Relative energy ($\text{kcal}\cdot\text{mol}^{-1}$).

fragmenting the TSs along the C8–C9 single bonds. The values obtained for the different TSs indicate that negligible charge transfer occurs from the alkenyl sulfoxide to the oxidopyrylium ylide.

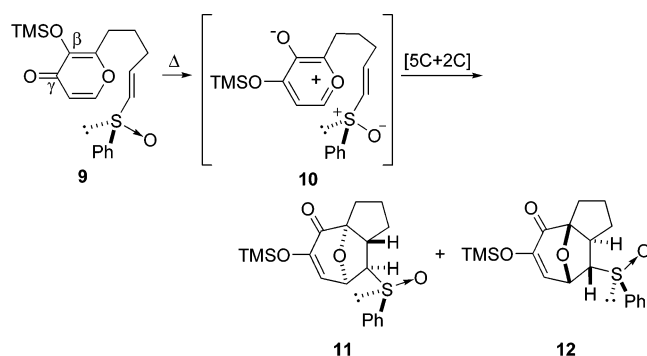
The values of the activation enthalpies, entropies, and Gibbs energies for the four different reaction channels were estimated using the potential energy barriers computed at the B3LYP/6-31G* level along with the B3LYP/6-31G* harmonic frequencies. The results are summarized in Table 5. It can be deduced from these results that the inclusion of the zero-point energy and thermal contributions does not affect the potential energy barrier differences between the relevant TSs.

Solvent Effects. The experimentally observed influence of the solvent polarity on the diastereoselectivity of the reaction is in consonance with the differences between the dipolar moments of the four transition structures, particularly between those in which the alkenyl sulfoxide is in an *s-cis* or *s-trans* conformation. Solvent effects were qualitatively estimated at the B3LYP/6-31G* level using the simple polarizable continuum model (PCM).¹⁴ We performed single-point calculations on the different transition states in toluene and acetonitrile, solvents for which the highest differences in diastereoselectivity were experimentally found. The results of these calculations are summarized in Table 6.

As can be observed, the energy difference between the two less energetic transition structures is only slightly lower in toluene than in the gas phase. However, in a solvent with a higher dielectric constant, such as acetonitrile, the transition states with an *s-cis* conformation and therefore with a higher dipole moment (**TS2** and **TS4**) are relatively less destabilized than the *s-trans* structures (**TS1** and **TS3**). This leads to an overall decrease in the energy gap between the most favorable TSs from $2.8 \text{ kcal}\cdot\text{mol}^{-1}$ in toluene to $1.9 \text{ kcal}\cdot\text{mol}^{-1}$ in acetonitrile. These theoretical data fully agree with our experimental findings that the diastereoisomeric ratio of the cycloaddition drops from 100:0 when the reaction is carried out in toluene to 85:15 when the more polar solvents acetonitrile and DMF are employed.

(17) Wiberg, K. B. *Tetrahedron* **1968**, *24*, 1083.

SCHEME 3



In summary, the diastereoselectivity observed in the sulfinyl-directed asymmetric thermal [5C + 2C] intramolecular cycloadditions between 6-acetoxy-3-pyranones and alkenes can be theoretically explained by means of B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G* calculations. The computational results suggest that the dipolar interactions between the sulfoxide and the oxidopyrylium ylides play a central role in attaining high diastereoselectivities in the cycloaddition by determining a predominant conformation of the alkenyl sulfinyl group in the transition state of the reaction.

β -Silyloxy- γ -pyrone/Alkene Cycloaddition. The results described above confirm the utility and value of DFT theoretical calculations to interpret the origin of the asymmetric induction in the intramolecular cycloaddition between alkenyl sulfoxides and acetoxy-pyranones. On the basis of these results, we were prompted to perform a similar theoretical analysis of the related intramolecular thermal [5C + 2C] cycloaddition between β -silyloxy- γ -pyranones and alkenyl sulfoxides. Domingo and co-workers recently showed that DFT calculations provide a suitable mechanistic interpretation of the cycloaddition between β -silyloxy- γ -pyranones and alkenes.⁴ Their analysis confirmed that the reaction proceeds through a stepwise process involving initial migration of the silyl group from the β - to the γ -position of the pyrone and a subsequent concerted cycloaddition between the generated oxidopyrylium ylide and the alkene. In a model system like **9** such a stepwise mechanism would involve the formation of the oxidopyrylium ylide **10**, which is a 4-silyloxy analogue of ylide **5**—the proposed intermediate in the previously discussed acetoxy-pyranone/alkenyl sulfoxide cycloaddition. Therefore, in principle, the diastereoselectivity of these asymmetric pyrone/alkene cycloadditions could be based on similar structural and energetic grounds. To verify this hypothesis and to ascertain more information about the energy profile of these asymmetric cycloadditions, a theoretical DFT study was performed on the cycloaddition of model pyrone **9** (Scheme 3).¹⁸

Our results indicate that the conversion of **9** to the oxidopyrylium ylide intermediate **10**, which is 11.1 kcal·mol⁻¹ higher in energy than **9**, involves **TS5** (Figure 4). The energetic barrier associated with this step is 13.3 kcal·mol⁻¹. Analysis of the rotational barriers around the C–S bond in intermediate **10** indicates that the *s-cis* conformer is 0.97 kcal·mol⁻¹ more stable than the *s-trans*

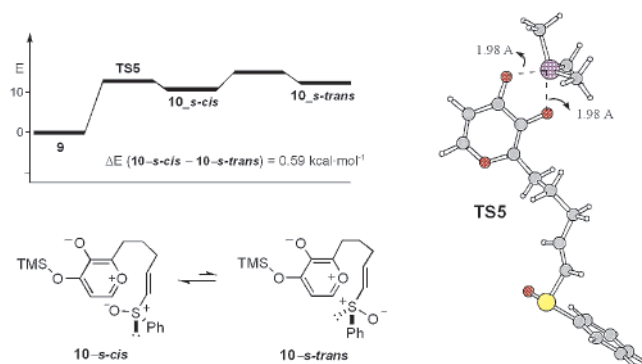


FIGURE 4. Potential energy profile of the oxidopyrylium-generating step in the cycloaddition of **9** (B3LYP/6-311+G**//B3LYP/6-31G*).

TABLE 7. Relative Energies (kcal·mol⁻¹) for the Stationary Points of the Asymmetric [5 + 2] Cycloaddition of **9**

	B3LYP/6-31G*	B3LYP/6-311+G**//B3LYP/6-31G*
9	-11.1	-11.7
10-s-cis	0	0
10-s-trans	0.97	0.59
TS6	14.9 (0) ^a	16.7 (0) ^a
TS7	16.4 (1.5) ^a	18.9 (2.2) ^a
TS8	17.5 (2.6) ^a	20.3 (3.6) ^a
TS9	17.8 (2.9) ^a	20.7 (4.0) ^a
11	-17.5	-14.3
12	-17.1	-15.0

^a Relative to **TS1**.

rotamer. This energy gap is reduced to 0.59 kcal·mol⁻¹ when the more precise basis set 6-311+G** is used to recalculate the energies of these two geometries.

An exhaustive analysis of the PES for the cycloaddition led us to characterize four possible concerted transition states analogous to those previously found for the 6-acetoxy-3-pyranone/alkenyl sulfoxide cycloaddition. The activation energies for these concerted TSs are given in Table 7 and their structures depicted in Figure 5.

The theoretical data show that in the less energetic TS, which leads to the major cycloadduct, the alkenyl sulfoxide is in an *s-trans* conformation and approaches the oxidopyrylium ylide from its less hindered face, i.e., opposite to the aryl group. The next favored TS leads to the minor adduct and corresponds to an *s-cis* conformation for the sulfinyl group. Finally, **TS8** and **TS9**—in which the phenyl group of the sulfoxide points toward the pyrone—are considerably higher in energy. The energetic difference between the four transition structures becomes even more marked when the precision of the calculation is increased (Table 7). In a similar way to the previously studied cycloadditions, the dipolar moments of the transition structures with the *s-trans* sulfinyl unit are significantly lower than those for the *s-cis* conformation. Although **TS8** presents the lowest μ value, steric factors make it much more energetic than **TS6**.

The characterization of the two possible cycloadducts completes the energetic profile of the cycloaddition from which the diastereodifferentiating step can clearly be observed (Figure 6).

Values for the activation enthalpies, entropies, and Gibbs energies corresponding to this diastereodifferen-

(18) To reduce the computational cost, the TBS, *p*-tolyl, and diethyl ester groups of **3a** were replaced by TMS, phenyl, and hydrogens, respectively.

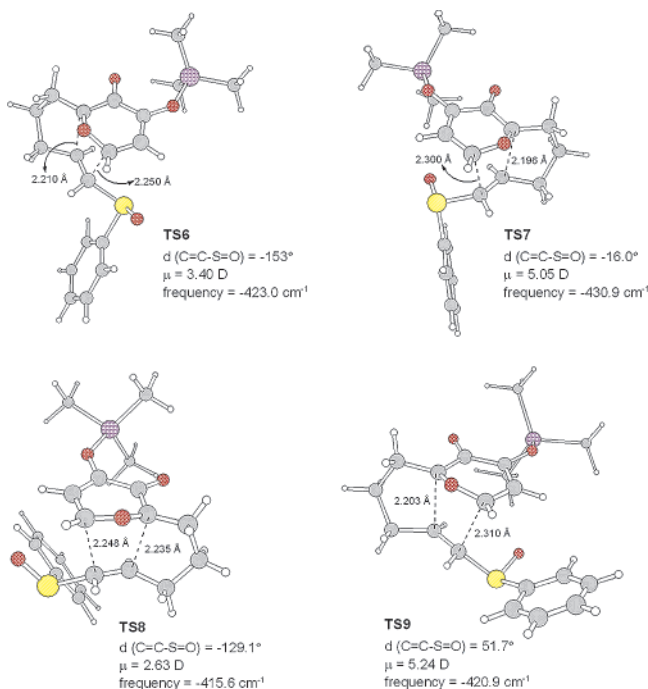


FIGURE 5. B3LYP/6-31G*-optimized geometries, dipolar moments (D), C=C-S=O dihedral angles (deg), and imaginary frequencies (cm⁻¹) for the transition structures **TS6-TS9**. The lengths of the C-C bonds involved in the reaction are given in angstroms.

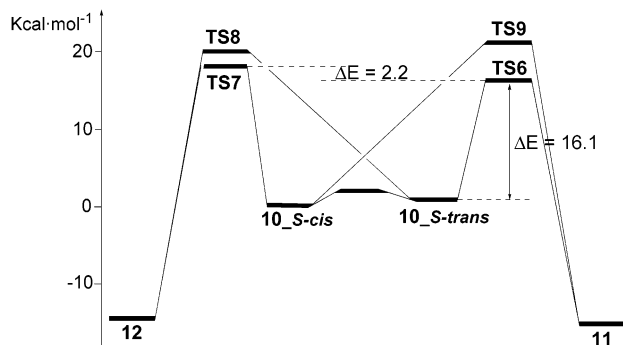


FIGURE 6. Potential energy profile for the cycloaddition of the oxidopyrylium ylide **10** (B3LYP/6-311+G**//B3LYP/6-31G*).

TABLE 8. Activation Enthalpies (kcal·mol⁻¹), Entropies (cal·mol⁻¹·K⁻¹), and Gibbs Energies (kcal·mol⁻¹) Computed at 110 °C and 1 atm for the Intramolecular Cycloaddition of **10** (B3LYP/6-31G*)

	ΔH^\ddagger	ΔS^\ddagger	ΔG^\ddagger
10-s-cis → TS6	13.78	-18.58	20.90 (0) ^a
10-s-cis → TS7	15.30	-19.03	22.59 (1.71) ^a
10-s-cis → TS8	16.52	-22.56	25.16 (4.26) ^a
10-s-cis → TS9	16.73	-21.07	24.80 (3.90) ^a

^a Relative to **10-s-cis** → **TS6**.

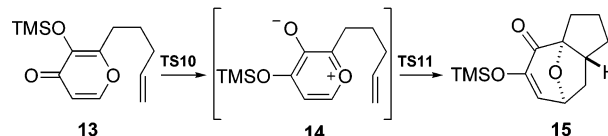
tiating step were also computed at 110 °C, which is the experimental temperature used to carry out the [5 + 2] cycloaddition (Table 8).

The relative values of these Gibbs activation energies predict a 91:9 ratio for product distribution, which fully agrees with the experimental data reported previously,

TABLE 9. Relative Energies (kcal·mol⁻¹) for the Stationary Points of the Intramolecular [5 + 2] Cycloaddition of **13**

	B3LYP/6-31G*	B3LYP/6-311+G**//B3LYP/6-31G*
13	0	0
TS10	13.9	13.1
14	12.0	11.9
TS11	28.0	30.2
15	-11.0	-7.0

SCHEME 4



where the diastereomeric ratios ranged from 91:9 to 97:3 depending on the linker employed to join the pyrone to the alkenyl sulfonamide.^{8b}

Finally, to elucidate the influence of the sulfinyl group on the rate of the reaction we calculated the energy profile for the cycloaddition of **13**, an alkene-unsubstituted analogue of **9**, at the B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G* levels of theory. Our results indicate that the activation barrier for the cycloaddition of the model pyrone **13** is 1.10 kcal·mol⁻¹ higher than the energy barrier for the asymmetric cycloaddition of sulfinyl-substituted homologue **9** (Table 9).¹⁹ This difference increases up to 1.60 kcal·mol⁻¹ when the most precise basis set (6-311+G**) was employed to recalculate the energy of the optimized structures. We can therefore conclude that this level of theory in addition to explain the high diastereoselectivity found in the thermal asymmetric cycloadditions of the alkenyl-sulfinyl-pyrone derivatives, is also able to qualitatively predict the higher reactivity compared to their desulfinylated analogues (Scheme 4).

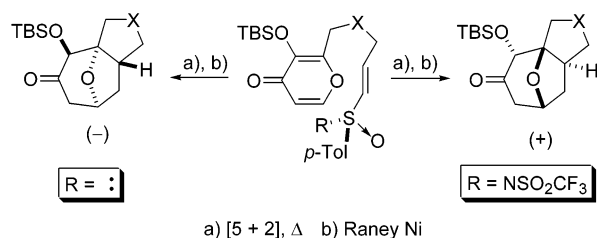
Reversal of Stereoselectivity in the Pyrone/Alkene Cycloadditions by Switching from Sulfoxide to Sulfoximine. We recently reported that the diastereofacial selectivity of these sulfinyl-directed pyrone/alkene cycloadditions can be reversed by transforming the sulfoxide into an appropriate sulfoximine.²⁰ Such a transformation can be readily performed with an aminating agent such as MSH (*O*-mesitylsulfonylhydroxylamine) and takes place with retention of configuration at the sulfur. The use of this switching tactic allows both enantiomers of the final oxabicyclic adducts to be readily synthesized from the same precursors (Scheme 5).

The reversal of the sense of asymmetric induction on switching from the sulfoxide to the trifluoromethane-sulfonesulfoximine was qualitatively explained by assuming that the introduction of the NR group on the sulfur induces a change in the conformational preferences of the sulfinyl group in the TS of the reaction. To decrease the dipolar and the steric interactions, the alkenyl sulfoximine might adopt in the most favored TS a conformation in which the S-O bond is syn coplanar to

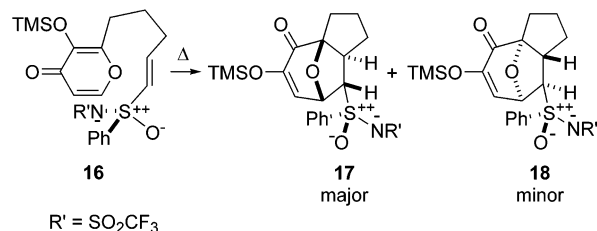
(19) Cycloadditions of the alkene-unsubstituted analogues required either longer reaction times at 110 °C (3–6 times longer) or higher temperatures. See ref 8 for more details.

(20) López, F.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2001**, *3*, 623.

SCHEME 5



SCHEME 6



the double bond (*s-cis*) and the S–N bond in an anti coplanar mode (*s-trans*), thereby inducing an inversion in the facial selectivity of the cycloaddition.

In an attempt to learn more about this possibility we investigated whether the level of theory employed to analyze the previously described cycloadditions could also explain this reversal of facial stereoselectivity. The reaction studied involved the simplified model **16** (Scheme 6).

The relatively large number of heavy heteroatoms considerably increases the computational cost of the process, and we therefore just focused our study on the DFT (B3LYP/6-31G*) characterization of the possible transition states. It can be observed from Figure 7 that the least energetic transition state found for this cycloaddition (**TS12**), which leads to the major cycloadduct **17**, has a conformation in which the alkenesulfonimidoyl group is in a disposition concordant with that we had previously hypothesized. Another TS structure (**TS13**) can be found more than 0.20 kcal·mol⁻¹ higher in energy. **TS13** has a C=C–S=O dihedral angle of approximately 160° and would lead to the minor diastereoisomer. Although this difference in energy seems to be slightly lower than expected given the observed experimental diastereoselectivities, the B3LYP/6-31G* calculations do predict, at least in a qualitative fashion, the reversal of the facial selectivity observed with respect to the cycloaddition of the sulfinyl analogue.

Analysis of the vibrational frequencies and the lengths of the bonds involved in the process suggest that, although this reaction is also a concerted process, the formation the bonds is much more asynchronous than the previously studied asymmetric [5 + 2] cycloadditions

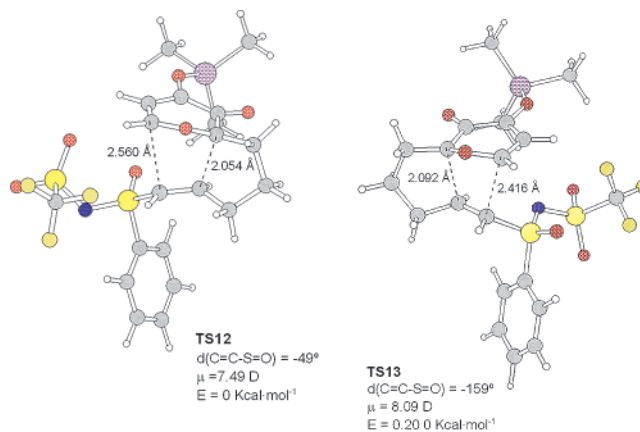


FIGURE 7. B3LYP/6-31G*-optimized geometries, dipolar moments (D), C=C–S=O dihedral angles (deg), and relative energies (kcal·mol⁻¹) for the transition structures **TS12**–**TS13**. The lengths of the C–C bonds involved in the reaction are given in angstroms.

directed by sulfoxides. This fact is probably due to the greater electron-withdrawing character of the sulfonimidoyl group, a property that induces a higher polarization of the double bond.

Conclusions

A computational DFT study (B3LYP/6-31G* and B3LYP/6-311+G**//B3LYP/6-31G*) has been carried out on the sulfinyl-directed asymmetric thermal [5C+2C] cycloadditions of 6-acetoxy-3-pyranones and β-silyloxy-γ-pyrone with alkenyl sulfoxides. The data obtained support our previous qualitative assumptions concerning the factors responsible for the facial stereoselection in these cycloadditions and confirm the importance of dipolar interactions between the sulfoxide group and the oxidopyrylium ylide dipoles in the transition states of the reactions. The success of DFT modeling in explaining the experimental results of the above [5C + 2C] cycloadditions suggest that this type of theoretical analysis could prove useful to predict the outcome of other sulfinyl-directed reactions.

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Supporting Information Available: Cartesian coordinates and computed energies of all the structures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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