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(±)-3,3-Diethoxycarbonyl-2-*p*-tolylsulfinylacrylonitrile as dienophile: relationship between the barrier for pyramidal inversion of vinyl sulfoxides and the electronic effects of the substituents at the double bond

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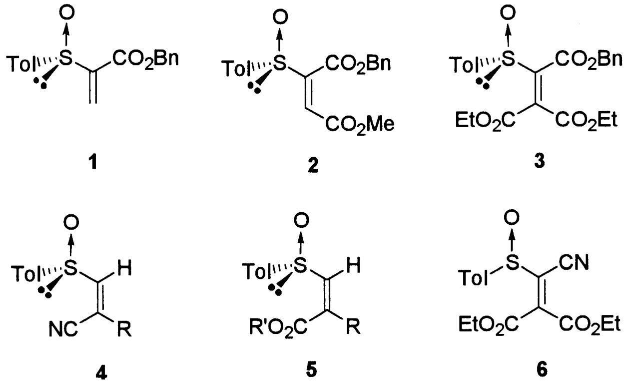
Abstract—The dienophilic behavior of (±)-3,3-diethoxycarbonyl-2-*p*-tolylsulfinylacrylonitrile (**6**) is reported and compared with that of trialkoxycarbonyl sulfinylethylene (**3**). The change of a CO_2R group by a CN one increases both the reactivity and the stereoselectivity of the cycloaddition. It seems that the linear structure of the CN group increases the planarity of the system reinforcing its electron-withdrawing power and therefore improving its dienophilic behavior. Otherwise, the low configurational stability at room temperature of the sulfoxide **6**, which is obtained as a racemic from its optically pure precursor, must also be a consequence of this strong electronic demand of the substituents which results in an unusually small energetic barrier for pyramidal inversion of the sulfinyl sulfur in compound **6** ($\Delta G^{\ddagger}=16.3$ kcal mol^{-1} at $T_c=25$°C, determined by dynamic NMR spectroscopy). This is the first evidence of the existing relationship between racemization barrier of vinyl sulfoxides and the electron-withdrawing power of the groups joined to the double bond. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The asymmetric Diels–Alder reaction is one of the most important methods to prepare optically enriched six membered ring systems due to its ability to create up to four chiral centers in one step with a high degree of stereocontrol.[1–5] The sulfinyl group has proved to be one of the most efficient chiral auxiliaries when located either at diene or dienophile, due to its ability to control the stereoselectivity of the cycloaddition process.[6–8] Concerning the use of sulfinylethylenes as dienophiles, their reactivity and *endo*-selectivity are both moderate or low unless they bear additional electron-withdrawing groups at the double bond, alkoxycarbonyl ones having been the most widely studied. In this field, one of us has described the Diels–Alder reactions of vinyl sulfoxides **1**,[9–11] **2**,[12–14] and **3**[15] (Scheme 1), which are mono, di, and trialkoxycarbonyl derivatives, respectively. The reactivity and stereoselectivity of sulfinylmaleates **2** were highly satisfactory, mainly when reactions were conducted under $TiCl_4$ catalysis,[12–14] but in the absence of this catalyst (which cannot be used with many acyclic dienes due to their polymerization) the reactivity is rather moderate (similar to that of **1**). Additionally, the low regioselectivity detected in the elimination of the sulfinyl group from the resulting adducts restricted their usefulness. The incorporation of a third alkoxycarbonyl group to the double bond was unable to solve these problems and thus compound **3** exhibited a reactivity lower than **2** and **1**, as well as low *endo*/*exo* and π-facial selectivities.[15] Two alternative explanations can be postulated to account for this behavior. The first one would assume that steric interactions hindering the coplanarity of the alkoxycarbonyl



Scheme 1.

Keywords: vinyl sulfoxides; Diels–Adler reactions; racemization; stereoelectronic effects.

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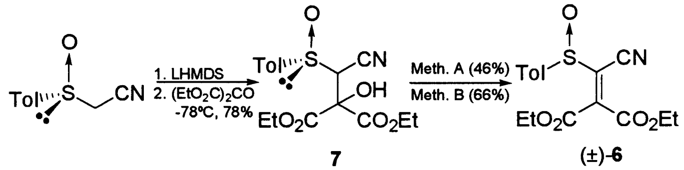


Method A: $(CF_3SO_2)_2O$, DIPEA, CH_2Cl_2 (-78°C);
Method B: MsCl, DIPEA, CH_2Cl_2 (-78°C)

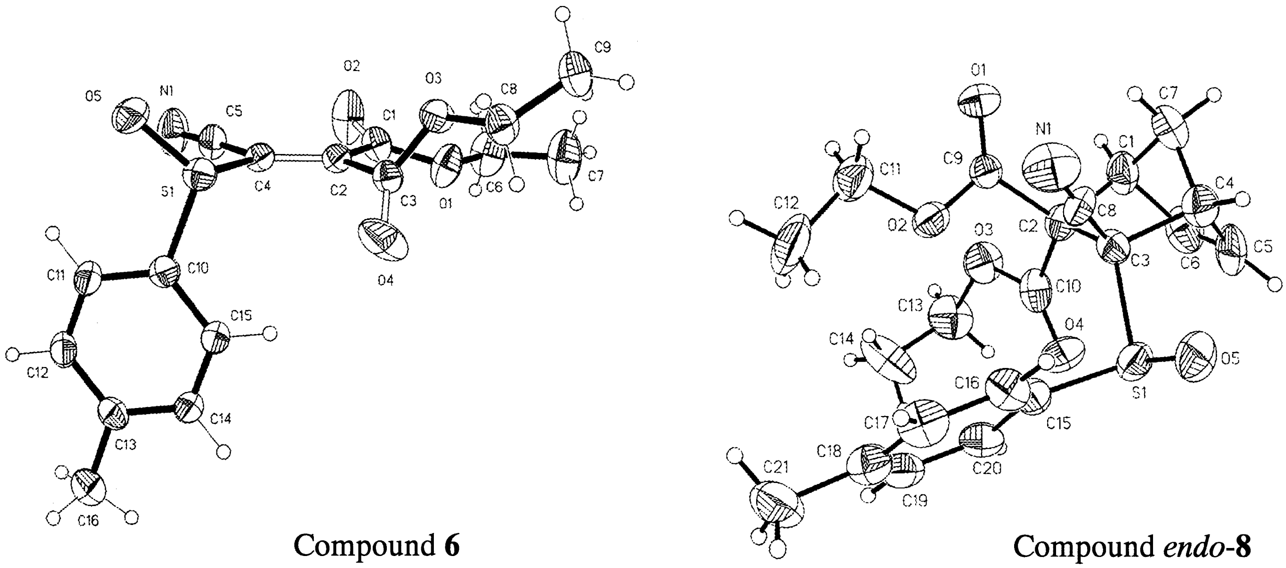
Scheme 2.

groups reduce their activating ability (as well as their *endo*-orientating character). Thus, the expected improvement in the reactivity when the number of the alkoxycarbonyl groups at the double bond increases, would be compensated by the decrease in their activating ability produced by the steric interactions distorting their coplanarity (such a distortion would be very important for trialcoxycarbonyl derivative **3**). The second explanation would involve the assumption that the sulfinyl group could act as an electron-donating or -withdrawing group depending on the nature of the other groups present at the double bond. This dual behavior would be due to the fact that the +M effect of the lone electron pair at the sulfinyl sulfur (whose electronic description usually only considers its −M and −I effects, thus only considering it as an electron-withdrawing group) was operative and eventually became its predominant electronic effect when it was required by other strongly electron-demanding groups at the double bond. According to this description, the sulfinyl group could be considered as a buffer of the electronic density of the double bond, and the increase in dienophilic reactivity expected from the increase in the number of groups such as esters at the double bond could be compensated by an inversion of the electronic influence of the sulfinyl group. Both explanations do not exclude each other.

In order to check the first explanation, the substitution of the ester groups by the cyano ones seemed to be appropriate because the linear structure of the latter suggested the absence of steric interactions with the flanking groups restricting their planarity. Thus we envisioned that sulfinylacrylonitriles should be better dienophiles than sulfinylacrylates, which could be demonstrated by studying the dienophilic behavior of several enantiopure (*Z*)-3-*p*-tolylsulfinylacrylonitriles **4**[16–17] (Scheme 1). The reactivity of these nitriles, although higher than that of the corresponding acrylates **5**,[18–22] was rather moderate thus suggesting that the increase in the reactivity produced by the nitrile could be partially compensated by the sulfinyl group, now acting as an electron donor group. In order to confirm this first evidence and thus clarify on the electronic behavior of the sulfinyl group, the study of other systems with more activated vinyl sulfoxides was necessary. In this sense we decided to study the dienophilic behavior of the 3,3-diethoxycarbonyl-2-*p*-tolylsulfinylacrylonitrile **6** because it has a structure similar to **3** but with a linear CN group instead of that of the trigonal alkoxycarbonyl groups, thus suggesting an improvement in reactivity and stereoselectivity. In this paper we report the results obtained in this study which confirm the above-mentioned assumptions and what is more important, we provide the first evidence of the existing relationship between the configurational stability of the vinyl sulfoxides and the electronic character of the substituents joined to the dienophilic double bond.

2. Results and discussion

The synthesis of 3,3-diethoxycarbonyl-2-*p*-tolylsulfinylacrylonitrile **6**, was carried out as depicted in Scheme 2,

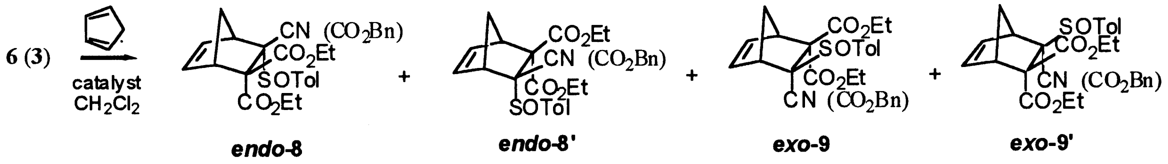


Compound **6**

Compound *endo*-**8**

Figure 1. X-Ray structures for compounds **6** and *endo*-**8**.

Table 1. Diels–Alder reactions of dienophiles **6** and **3** (values in brackets taken from Ref. 15) with cyclopentadiene



Entry	Catalyst (1.2 equiv.)	*T* (°C)	*t* (h)	Yield (%)[a]	*endo*-**8**[b]	*endo*-**8′**[b]	*exo*-**9**[b]	*exo*-**9′**[b]	*endo*/*exo*Ratio
1	–	20 (20)	2.5 (72)	80 (83)	80 (62)	–(8)	20 (30)	–(–)	4.0 (2.3)
2	Eu(fod)$_3$	−20 (0)	2 (2)	79 (77)	89 (62)	–(8)	11 (30)	–(–)	8.1 (2.3)
3	ZnBr$_2$	−20 (−10)	2 (2)	84 (89)	92 (55)	–(–)	8 (45)	–(–)	11.5 (1.2)
4	TiCl$_4$	−78 (−78)	–[c](1)	–[c](76)	–[c](90)	–[c](4)	–[c](6)	–[c](–)	–[c](15.6)

[a] Of pure adducts after chromatographic purification.

[b] Isomer ratio determined by ^{1}H NMR.

[c] Slow decomposition of the dienophile **6** was observed in the presence of this catalyst.

using a synthetic sequence parallel to that used for the preparation of **3**.[15] Deprotonation of (*R*)-(+)-cyanomethyl-*p*-tolyl sulfoxide[23] with LHMDS (1.2 equiv.) in THF and further reaction of the resulting anion with diethyl oxomalonate at −78°C furnished the diastereomerically pure (its configuration was not determined) alcohol **7** in 78% yield after flash chromatography. Dehydration of **7** was performed by treatment with triflic anhydride–diisopropylethylamine or with MsCl–diisopropylethylamine in CH_2Cl_2 at −78°C affording the pure vinyl sulfoxide **6** in 46 and 66% yield, respectively (after chromatography). Surprisingly, the optical purity of **6** [$[\alpha]_D=+0.9$ (*c* 1, acetone)] was very low (ee≤5%, determined by ^{1}H NMR in the presence of Yb(hfc)$_3$), despite its precursor **7** was optically active [$[\alpha]_D=+93.4$ (*c* 1, acetone)]. We will return to this interesting finding later.

The X-ray diffraction analysis of **6** (Fig. 1), which confirms its racemic nature,[24] reveals that the ester group in *cis*-arrangement with respect to the CN one is almost coplanar with the double bond (the dihedral angle C_4–C_2–C_1–O_2= 17°, Fig. 1) thus confirming our predictions about the scarce influence exerted by the linear cyano group in the conjugation of the flanking groups. By contrast, the planarity of the second ester group is strongly restricted (dihedral angle C_4–C_2–C_3–O_4=58.5°), maybe due to its steric and electronic interactions with the flanking sulfinyl and ester groups. Finally, the conformational arrangement around the C–S bond is the one wherein the *p*-tolyl group is oriented in an almost perpendicular plane (dihedral angle C_2–C_4–S_1–C_{10}=−110°) with respect to that of the dienophilic double bond and the sulfinyl oxygen O(5) is oriented towards a face different to that of the carbonyl oxygen O(4). This conformation, which determines the steric course of the cycloadditions of compound **6** (see later), could also be predominant in solution as it minimizes the electronic repulsion between O(4) and O(5).

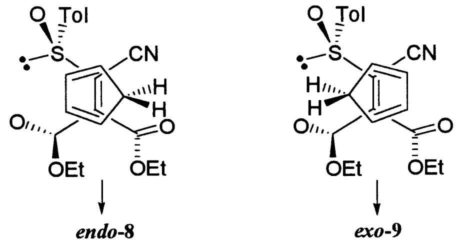
The results obtained in reactions of dienophile **6** with an excess of cyclopentadiene using CH_2Cl_2 as the solvent, under different conditions, are presented in Table 1. We have also included, for comparative purposes, the results obtained from enantiopure triester **3** under similar conditions.[15] In order to make easier this comparison, the *endo* or *exo* terms used in this paper describe the approach modes of the reagents or the stereochemistry of the adducts using as a reference the sulfinyl group (present in **3** and **6**), despite the right name could be the opposite according to the sequence rules.

From the results depicted in Table 1, it can be established that the reactions of dienophile **6** with cyclopentadiene under different conditions yielded a mixture of only two adducts (*endo*-**8** and *exo*-**9**), which were separated and purified by column chromatography. The *endo* structure and the configuration of the major adduct (**8**)[24] were unequivocally determined by an X-ray diffraction study (Fig. 1).

The stereochemistry of the minor adduct **9** was established as *exo* from the fact that the sulfone **11**, resulting from its oxidation with *m*-CPBA, exhibits a ^{1}H NMR spectrum different to sulfone **10** obtained by oxidation of sulfoxide *endo*-**8**, which revealed that both sulfones must display different *endo* or *exo* configuration. It allowed us to assign the *exo* stereochemistry to compound **11** and therefore to its precursor **9**, because that for **10** must be *endo* since it derives from *endo*-**8**. The complete π-facial selectivity observed in these reactions for the *endo* approach suggests that diastereotopic dienophilic faces must be clearly different, which must also be the case for the *exo* approach. Therefore, we could expect that the diene attack was predominant to the same face in both *endo* and *exo* approaches. It allowed to assign compound *exo*-**9** the relative configuration shown in Table 1.

The comparison of the results obtained from **6** with those from **3** (see Table 1 and Ref. 15), indicates that the reactivity of **6** is the highest one, but the most significant difference is observed in the stereoselectivity (see Table 1), compound **6** exhibiting a complete π-facial selectivity in both *endo* and *exo* approaches (in compound **3** this was the case only for the *exo* approach), and an *endo*/*exo* selectivity higher than those observed for compound **3**, mainly in the presence of catalysts such as Eu(fod)$_3$ and ZnBr$_2$ (entries **2** and **3**, Table 1).

Taking into account that the planarity of the three alkoxycarbonyl groups at **3** must be distorted due to steric and electronic interactions, hence minimizing their influence in the reactivity of the double bond, the higher reactivity

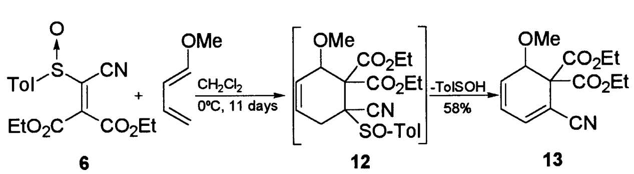


Scheme 3.

of compound **6** can be easily explained by assuming that it must adopt a similar spatial arrangement in solution and in the solid state (see Fig. 1), the CN group scarcely affecting the planarity of the flanking ester, which will be more efficient in increasing the dienophilic reactivity.

Concerning the stereoselectivity, the complete π-facial selectivity observed in the cycloaddition of nitrile **6** in both *endo* and *exo* approaches, is not unexpected if we take into account the almost normal arrangement of the aryl group and the orientation of O(4), which completely precludes the approach of the diene from the face that they both occupy (Fig. 1). On the other hand, the clear predominance of the *endo* sulfinyl approach is intriguing. From an electronic point of view, it could be expected that the *endo* orientating character of the CN and ester groups in a *cis*-arrangement—the latter almost coplanar with the double bond—were higher than that of the SOTol and CO_2Et group lacking such planarity. We assume that the interactions between the methylene bridge of the cyclopentadiene with the sulfinyl and alkoxycarbonyl oxygens O(3) and O(5), oriented towards the face suffering the diene approach yielding *exo*-**9**, are the main responsible for the observed preference for the *endo* sulfinyl approach (Scheme 3). The increase in the *endo* selectivity in the presence of Lewis acids, which are able to associate with such oxygens (mainly the sulfinyl one), thus increasing their size and therefore the magnitude of their steric interactions, reinforces this explanation.

Next, we studied the reactions of **6** with 1-methoxy-1,3-butadiene and Danishefsky's diene. These reactions were carried out under thermal conditions (Schemes 4 and 5).

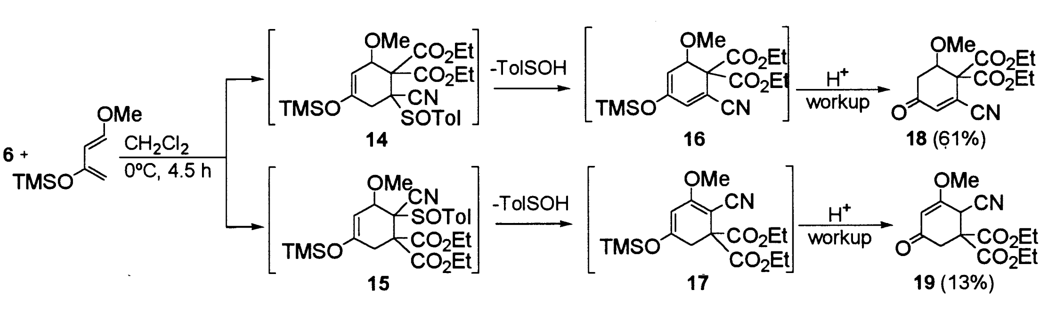


Scheme 4.

As in the case of the reactions of dienophiles **2**[12–14] and **3**[15] with acyclic dienes, the adducts derived from **6** were not stable and rapidly evolved to the desulfinylated compounds resulting from the *syn*-pyrolytic elimination of the sulfinyl group. As depicted in Scheme 4, the cycloaddition of **6** with 1-methoxy-1,3-butadiene gave the adduct **12**, which could not be detected and rapidly evolved into the cyclohexadiene **13**, obtained as the sole product in 58% yield. This evolution, which precludes to obtain any stereochemical information, indicates that the regioselectivity of the reaction is complete and exclusively controlled by the vinyl carbon supporting the *gem*-diester function. This regioselectivity is not unexpected because it is just the same to that observed with dienophile **3**. On the other hand, the Diels–Alder reaction of **6** with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene afforded the regioisomers **18** and **19** in 61 and 13% yields, respectively (Scheme 5), the formation of which can be explained by spontaneous desulfinylation of the initially formed adducts **14** and **15** and concomitant hydrolysis of the resulting enol silyl ethers **16** and **17** during the work-up.

The decrease in the regioselectivity observed for the 1,3-disubstituted diene is unexpected from an electronic point of view (both substituents reinforce the same orientation), which suggests that steric factors involving the substituent at C-3 in the diene and those of the dienophile in the favored *endo* or *exo* approach must be significant in the regioselectivity control.

The surprising racemization observed in the formation of compound **6** from its optically active precursor **7** is a fact that had some precedents. Thus it had been previously observed in the synthesis of *trans*-3-*p*-tolylsulfinyl-2-propenal.[25] In this case we were not able to find reproducible reaction conditions allowing the preparation of the optically pure compound. A similar but fortunately easy to control situation was observed in the synthesis of cyclic vinyl-*p*-tolylsulfilimines.[26] Taking into account that reaction conditions used in the synthesis of these compounds were not stronger enough to justify a chemical racemization, but all of them exhibit strong electron-withdrawing groups connected to the double bonds, we reasoned that the lack of optical activity could be a consequence of the decrease in the energetic barrier for the inversion at the sulfinyl sulfur. In order to evaluate such a barrier we have realized a NMR experiment.



Scheme 5.

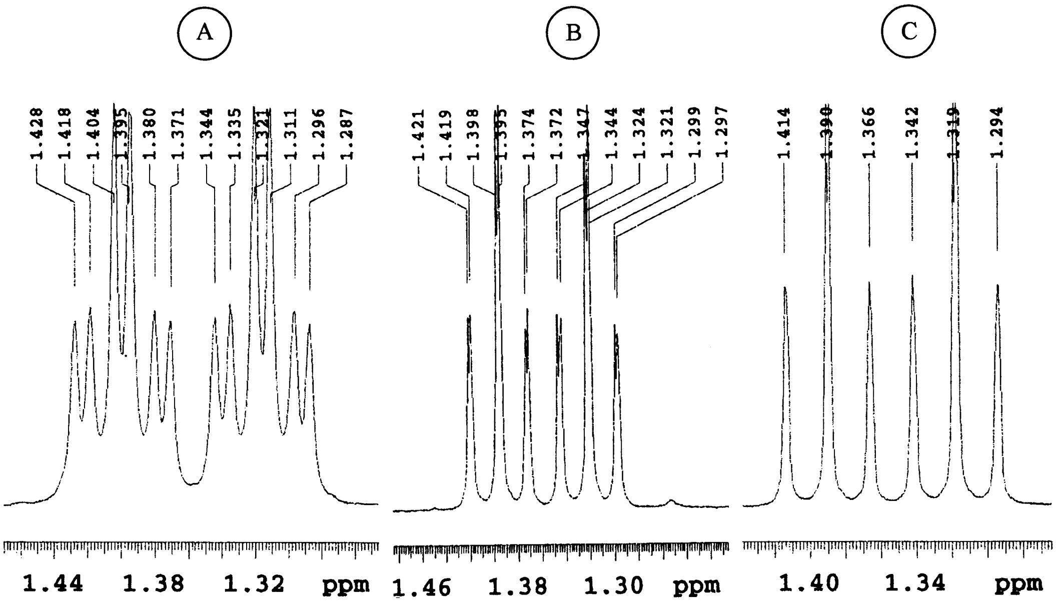


Figure 2. 300 MHz ^{1}H NMR signals of the methyl protons of the ethyl ester groups of (±)-**6** in the presence of two-fold molar amount of (−)-TFAE in $CDCl_3$. (A): at −60°C. (B): at 0°C. (C): at 25°C.

It is known that a number of compounds cannot be obtained in their optically pure form because of their rapid interconversion of its enantiomers at room temperature. Although the chirality of the enantiomers in racemic mixtures cannot be proved by optical methods, it can be demonstrated indirectly by dynamic NMR spectroscopy by using an appropriate chiral solvating agent.[27] Thus, different NMR spectra can be observed for enantiomers which undergo a sufficiently strong interaction with a optically active compound. By measuring nonequivalence as a function of the temperature it is possible to determine the interconversion rates of enantiomers.[28] This approach has been used to determine the barrier to pyramidal inversion of the enantiomers of **6**. The ^{1}H NMR signals of the methyl protons of the ethyl ester groups of (±)-**6** in $CDCl_3$ at 300 MHz in the presence of two molar equivalents of (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol [(−)-TFAE] at three different temperatures are presented in Fig. 2. As it can be observed, at −60°C (Fig. 2(A)), the triplets of the methyl protons of the two enantiomers appears splitted with a $\Delta\delta=3$ Hz. An increase in the temperature causes a rapid interconversion (Fig. 2(B)) and the methyl signals coalesce at 25°C (Fig. 2(C)). If the coalescence temperature T_c is 25°C, from these values we obtain a rate constant $k_c=6.6\ s^{-1}$ and $\Delta G^{\ddagger}=16.3\ kcal\ mol^{-1}$.

The unexpectedly low $\Delta G^{\ddagger}$ value for pyramidal inversion of the sulfinyl sulfur (for dialky, diaryl, and alkyl aryl sulfoxides the values are $\Delta G^{\ddagger}=35–42\ kcal\ mol^{-1}$)[29] must be related to the electronic influence of the substituents at the double bond in compound **6**. The increase in the planarity of the system enhances the electron-withdrawing power of the substituents, thus favoring that the lone electron pair at sulfur was shifted towards the double bond, in order to compensate for its electronic deficiency. It determines that the sulfinyl group can exhibit a +M effect, which is not usually considered. Two are the consequences of this electronic shifting. First of all, the planarity of the sulfinyl sulfur must increase (the conjugation of the lone electron pair at sulfur is more efficient when it occupies a p orbital of one planar sp^2 hybridized sulfur) thus lowering its energetic barrier for the pyramidal inversion, as it is observed. Additionally the fact that the sulfinyl group becomes as electron-donating in this and similar compounds, can contribute to decrease their dienophilic reactivity, as it has also been observed (Section 1). A systematic study about the influence of different electron-withdrawing groups on the racemization barrier of the vinyl sulfoxides is in course and will be published in further papers.

3. Conclusion

In summary, we have demonstrated that the substitution of one of the alkoxycarbonyl groups of the triester **3** by the cyano one improves both reactivity and stereoselectivity. On the other hand, the presence of strongly electron-withdrawing groups at the double bond of vinyl sulfoxides causes a decrease in the energy barrier for the pyramidal inversion of the sulfinyl sulfur, thus making its racemization easier. This is the first evidence about the influence of the electronic effects of the substituents at double bond in the configurational stability of vinyl sulfoxides.

4. Experimental

4.1. General

Melting points were determined in a Culatti apparatus. All moisture sensitive reactions were performed in flame-dried glassware equipped with rubber septa under positive argon pressure and monitored by TLC. Solvents were dried according to literature procedures. Optical rotations were measured on a digital polarimeter at 20°C (concentration in g/100 mL). ^{1}H and ^{13}C NMR spectra were obtained at

300 and 75 MHz, respectively, on deuterochloroform using TMS as the internal standard. Mass spectra were measured at 70 eV and 190°C.

Analytical thin layer chromatography was performed on Alugram 0.25 mm silica gel 60 sheets (Macherey–Nagel). Visualization was accomplished with UV light absorption, iodine vapor or ethanolic fosfomolybdic acid solution followed by heating. Flash chromatography was performed with silica gel 60 Merck, (230–400 mesh). (*R*)-(+)-cyanomethyl-*p*-tolyl sulfoxide was prepared as described.[23]

4.1.1. (R_S)-(+)-3,3-Diethoxycarbonyl-3-hydroxy-2-*p*-tolylsulfinylpropionitrile (7). A solution of (*R*)-(+)-cyanomethyl-*p*-tolyl sulfoxide (1.0 g, 5.6 mmol, 1.0 equiv.) in THF (10 mL) was added, under argon, to a solution of LHMDS (prepared from a 1.1 M solution of *n*-BuLi (6.7 mmol, 1.2 equiv.) and hexamethyldisilazane (1.42 mL, 6.7 mmol, 1.2 equiv.) in THF (40 mL) at 0°C) cooled at −78°C. After stirring for 30 min, a solution of diethyl oxomalonate (0.945 mL, 6.2 mmol, 1.1 equiv.) was slowly added. Stirring was continued at −78°C for 2 h. Then, a saturated ammonium chloride solution (16 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (hexane–ethyl acetate 60:40) to produce 1.52 g (78%) of **7** as white crystals, mp 121–124°C, $[\alpha]_D=+93.4$ (*c* 1, acetone). IR ($CHCl_3$): 3496, 2987, 2941, 2908, 2248, 1764, 1747, 1597, 1066 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30 (t, $J=7.2$ Hz, 3H), 1.39 (t, $J=7.2$ Hz, 3H), 1.65 (bs, 1H, interchangeable with D_2O), 2.46 (s, 3H), 4.27–4.47 (m, 4H), 4.59 (s, 1H), 7.40 and 7.72 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$): δ 13.8, 14.0, 21.6, 62.1, 64.2, 64.3, 77.3, 112.3, 125.4, 130.3, 137.7, 144.1, 166.4, 166.6. EIMS: 353 (M^+, 18), 139 (100), 131 (10), 91 (12), 77 (4).

4.1.2. (±)-3,3-Diethoxycarbonyl-2-*p*-tolylsulfinylacrylonitrile (6). *Method A*. To a solution of **7** (1.34 g, 3.8 mmol, 1 equiv.) in CH_2Cl_2 (25 mL) stirred at −78°C under argon, triflic anhydride (0.912 mL, 4.18 mmol, 1.1 equiv.) and diisopropylethylamine (1.32 mL, 7.6 mmol, 2 equiv.) were successively added. The mixture was stirred at −78°C for 1 h, and then H_2O (30 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (hexane–ethyl acetate 80:20) to give a solid that was recrystallized from hexane–CH_2Cl_2 to produce 0.584 g (46%) of **6** as yellow crystals, mp 102–104°C.

Method B. To a solution of **7** (1.64 g, 4.7 mmol, 1 equiv.) in CH_2Cl_2 (65 mL) stirred at −78°C under argon, mesyl chloride (1.46 mL, 18.8 mmol, 4 equiv.) and diisopropylethylamine (3.24 mL, 18.8 mmol, 4 equiv.) were added. The mixture was stirred at −78°C for 2 h. Usual work-up and purification as above described produced 0.934 g (66%) of **6** as yellow crystals, mp 102–104°C. IR ($CHCl_3$): 2960, 2939, 2875, 2250, 1735, 1650, 1595, 1033 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, $J=7.2$ Hz, 3H), 1.41 (t, $J=7.2$ Hz, 3H), 2.44 (s, 3H), 4.36 (dq, $J=3.0$, 7.2 Hz, 2H), 4.46 (q, $J=7.2$ Hz, 2H), 7.39 and 7.79 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$): δ 13.7, 14.0, 21.6, 63.7, 63.8, 109.0, 125.3, 130.6, 136.8, 139.4, 144.0, 159.5, 161.1. EIMS: 335 (M^+, 10), 139 (100), 123 (10), 91 (13), 77 (6). Anal. Calcd for: $C_{16}H_{17}NO_5S$: C, 57.30; H, 5.11; N, 4.18. Found: C, 57.52; H, 5.20; N, 4.31.

4.2. Diels–Alder reactions of 6 with cyclopentadiene

Uncatalyzed reaction. To a solution of **6** (0.1 g, 0.30 mmol, 1 equiv.) in CH_2Cl_2 (2 mL), at room temperature under argon, cyclopentadiene (149 μL, 1.79 mmol, 6 equiv.) was added. The resulting solution was stirred for 2.5 h. Evaporation of the volatiles under vacuum afforded a residue that was analyzed by ^{1}H NMR (*endo*-**8**/*exo*-**9** ratio=80:20). The **8** and **9** isomers were separated and purified by flash chromatography using hexane–ethyl acetate 85:15 as the eluent.

Lewis acid promoted reactions. A solution of **6** (0.05 g, 0.15 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added to a suspension of the Lewis acid (0.18 mmol, 1.2 equiv.) in CH_2Cl_2 (2 mL) cooled at −20°C, under argon. The mixture was stirred for 10 min, and then 75 μL (89 mmol, 6 equiv.) of cyclopentadiene was added. Stirring was continued for 2 h at −20°C. After the addition of 5% HCl ($Eu(fod)_3$) or 10% $NaHCO_3$ ($ZnBr_2$), the aqueous layer was separated and extracted with CH_2Cl_2. The combined organic extracts were washed with water, dried, and concentrated. The obtained mixtures (see Table 1) were analyzed by ^{1}H NMR, separated and purified by flash chromatography.

4.2.1. (±)-(1*R*,2*S*,4*S*)-3,3-Diethoxycarbonyl-2-(*p*-tolylsulfinyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (*endo*-8). Mp 111–113°C (dec.). IR ($CHCl_3$): 3003, 2996, 2939, 2231, 1738, 1463, 1049 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.87 (t, $J=7.2$ Hz, 3H), 1.27 (t, $J=7.2$ Hz, 3H), 1.93 (dt, $J=1.8$, 10.2 Hz, 1H), 2.20 (dt, $J=1.5$, 10.2 Hz, 1H), 2.40 (s, 3H), 3.68 (m, 1H), 3.82 (m, 1H), 3.98 (m, 2H), 4.22 (m, 2H), 6.35 (dd, $J=3.0$, 5.7 Hz, 1H), 6.76 (dd, $J=3.0$, 5.7 Hz, 1H), 7.30 and 7.93 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$): δ 13.2, 14.0, 21.4, 47.7, 52.8, 54.5, 62.5, 63.9, 69.1, 76.4, 117.0, 127.3, 129.1, 137.2, 138.2, 139.5, 142.2, 167.1, 167.4. EIMS: 402 (M^++1, 8), 401 (M^+, 7), 385 (20), 262 (88), 234 (69), 206 (100), 188 (73), 144 (50), 123 (30), 91 (23). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.82; H, 5.77; N, 3.49. Found: C, 62.58; H, 5.80; N, 3.42.

4.2.2. (±)-(1*S*,2*S*,4*R*)-3,3-Diethoxycarbonyl-2-(*p*-tolylsulfinyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (*exo*-9). Mp 93–95°C (dec.). IR ($CHCl_3$): 3003, 2996, 2939, 2236, 1737, 1598, 1194, 1081 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.03 (t, $J=7.2$ Hz, 3H), 1.31 (t, $J=7.2$ Hz, 3H), 1.61 (t, $J=1.8$ Hz, 1H), 1.64 (t, $J=1.8$ Hz, 1H), 2.43 (s, 3H), 3.58 (m, 2H), 4.04 (m, 2H), 4.31 (q, $J=7.2$ Hz, 2H), 6.39 (dd, $J=3.0$, 5.4 Hz, 1H), 6.58 (dd, $J=3.0$, 5.4 Hz, 1H), 7.35 and 7.84 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$): δ 13.5, 13.9, 21.5, 44.9, 50.6, 52.1, 62.4, 63.1, 69.4, 71.7, 116.5, 127.3, 129.4, 137.5, 137.7, 140.8, 143.2, 166.4, 167.8. EIMS: 401 (M^+, 6), 385 (17), 262 (82), 234 (65), 206 (100), 188 (75), 144 (53), 123 (40), 91 (20). Anal. Calcd for $C_{21}H_{23}NO_5S$: C, 62.82; H, 5.77; N, 3.49. Found: C, 62.68; H, 5.82; N, 3.47.

4.3. General method for the oxidation of sulfoxides *endo*-8 and *exo*-9

To a stirred solution of *m*-CPBA (80–85%) (0.054 g, 0.25 mmol, 2 equiv.) in CH_2Cl_2 (2 mL) at 0°C a solution of sulfoxide (**8** or **9**) (0.050 g, 0.12 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added. The mixture was stirred at 0°C for 6 h. Then, a 10% $Na_2S_2O_3$ solution (5 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with water (5 mL), brine (5 mL), dried (Na_2SO_4), and evaporated under vacuum. The residue was purified by flash chromatography using hexane–ethyl acetate 75:25 as the eluent to yield **10** (82%) and **11** (80%), respectively.

4.3.1. (±)-(1*R*,2*S*,4*S*)-3,3-Diethoxycarbonyl-2-(*p*-tolylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (10). Mp 120–122°C. IR ($CHCl_3$): 3003, 2987, 2935, 2235, 1743, 1597, 1341, 1254, 1154 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, *J*=7.2 Hz, 3H), 1.30 (t, *J*=7.2 Hz, 3H), 1.67 (dt, *J*=10.2, 1.8 Hz, 1H), 1.96 (d, *J*=10.2 Hz, 1H), 2.47 (s, 3H), 3.16 (m, 1H), 3.70 (m, 1H), 4.20–4.40 (m, 4H), 6.35 (dd, *J*=3.0, 5.4 Hz, 1H), 6.64 (dd, *J*=3.0, 5.4 Hz, 1H), 7.40 and 8.02 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$): δ 13.7 (2C), 21.7, 46.9, 51.6, 56.3, 62.7, 63.3, 71.5, 74.4, 118.3, 129.6, 130.8, 133.1, 135.1, 139.1, 146.1, 165.1, 167.3. EIMS: 417 (M$^+$, 3), 372 (4), 306 (22), 262 (67), 216 (100), 188 (23), 170 (74), 144 (12), 139 (38), 91 (42).

4.3.2. (±)-(1*S*,2*S*,4*R*)-3,3-Diethoxycarbonyl-2-(*p*-tolylsulfonyl)bicyclo[2.2.1]hept-5-ene-2-carbonitrile (11). Mp 125–128°C. IR ($CHCl_3$): 3003, 2986, 2939, 2240, 1744, 1597, 1340, 1255, 1153 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, *J*=7.2 Hz, 3H), 1.34 (t, *J*=7.2 Hz, 3H), 1.68 (dt, *J*=10.2, 1.5 Hz, 1H), 2.49 (s, 3H), 2.72 (dt, *J*=10.2, 1.5 Hz, 1H), 3.17 (m, 1H), 3.75 (m, 1H), 4.18–4.42 (m, 4H), 6.33 (dd, *J*=3.0, 5.4 Hz, 1H), 6.39 (dd, *J*=3.0, 5.4 Hz, 1H), 7.42 and 7.98 (AA′BB′ system, 4H). ^{13}C NMR ($CDCl_3$): δ 13.6, 13.8, 21.8, 45.5, 52.0, 54.3, 62.7, 63.3, 68.8, 73.7, 116.8, 129.9, 131.1, 133.5, 138.4, 140.1, 146.5, 166.2, 166.3. EIMS: 417 (M$^+$, 4), 372 (3), 306 (14), 262 (95), 234 (32), 216 (100), 206 (48), 170 (45), 144 (36), 139 (27), 91 (45).

4.4. Diels–Alder reactions of 6 with acyclic dienes

To a solution of **6** (0.102 g, 0.30 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) cooled at 0°C, the corresponding diene (1.80 mmol, 6 equiv.) was added. The resulting solution was stirred at 0°C for 11 days in the case of 1-methoxy-1,3-butadiene, and 4.5 h in the case of *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene. The volatiles were removed under vacuum and the residue was purified by flash chromatography using hexane–ethyl acetate 80:20 as the eluent.

4.4.1. (±)-1-Cyano-6,6-diethoxycarbonyl-5-methoxy-1,3-cyclohexadiene (13). It was obtained, as the only product, from the reaction of **6** with 1-methoxy-1,3-butadiene. Yield: 58%, mp 59–62°C. IR ($CHCl_3$): 2989, 2937, 2830, 2221, 1737, 1263, 1082 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, *J*=7.2 Hz, 3H), 1.33 (t, *J*=7.2 Hz, 3H), 3.38 (s, 3H), 4.20–4.40 (m, 4H), 4.67 (d, *J*=5.1 Hz, 1H), 6.22 (dd, *J*=5.7, 9.6 Hz, 1H), 6.40 (ddd, *J*=0.6, 5.1, 9.6 Hz, 1H), 6.86 (dd, *J*=0.6, 5.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 13.7, 13.9, 57.0, 59.6, 62.5, 62.7, 72.4, 108.6, 117.7, 123.7, 129.2, 138.7, 165.3, 165.4. EIMS: 279 (M$^+$, 7), 372 (4), 206 (100), 178 (70), 160 (73), 148 (30), 130 (77), 102 (20).

4.4.2. (±)-3-Cyano-4,4-diethoxycarbonyl-5-methoxy-2-cyclohexen-1-one (18). It was obtained from the reaction of **6** with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene. Yield: 61%, mp 71–74°C. IR ($CHCl_3$): 2986, 2938, 2832, 2250, 1741, 1704, 1260, 1094 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.34 (t, *J*=7.2 Hz, 3H), 1.35 (t, *J*=7.2 Hz, 3H), 2.97–3.01 (m, 2H), 3.32 (s, 3H), 4.28–4.45 (m, 4H), 4.54 (t, *J*=3.0 Hz, 1H), 6.68 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.7, 13.9, 38.3, 57.4, 60.5, 63.1, 63.6, 78.6, 115.9, 124.3, 140.5, 164.5, 164.8, 192.8. EIMS: 295 (M$^+$, 12), 222 (100), 194 (58), 181 (42), 164 (55).

4.4.3. (±)-4-Cyano-5,5-diethoxycarbonyl-3-methoxy-2-cyclohexen-1-one (19). It was obtained from the reaction of **6** with *trans*-1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene. Yield: 13%, oil. IR ($CHCl_3$): 2983, 2940, 2250, 1739, 1670, 1623, 1456, 1349 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, *J*=7.2 Hz, 3H), 1.33 (t, *J*=7.2 Hz, 3H), 3.00 and 3.22 (AB system, *J*=17.1 Hz, 2H), 3.82 (s, 3H), 4.20–4.39 (m, 4H), 4.40 (s, 1H), 5.45 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 13.8, 13.9, 36.4, 39.2, 56.7, 57.3, 63.4, 63.5, 103.4, 114.6, 165.9, 166.7, 167.7, 191.9. EIMS: 295 (M$^+$, 10), 222 (100), 194 (97), 176 (72), 150 (30), 123 (61).

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References

1. Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 876.
2. Masamune, S.; Choy, W.; Petersen, J. S.; Sita, R. L. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.
3. Helmchen, G.; Karge, R.; Weetman, J. *Modern Synthetic Methods*; Sheffold, R., Ed.; Springer: Berlin, 1986; Vol. 4, p. 262.
4. Chapuis, C.; Jurczak, J. *Helv. Chim. Acta* **1987**, *70*, 436.
5. Kagan, H. B.; Riant, O. *Chem. Rev.* **1992**, *92*, 1007.
6. García Ruano, J. L.; Cid, B. *Topics in Current Chemistry*; Page, P. C. B., Ed.; Springer: Berlin, 1999; Vol. 204, p. 1.
7. Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717.
8. Aversa, M. C.; Barattucci, A.; Bonaccorsi, P.; Gianneto, P. *Tetrahedron: Asymmetry* **1997**, *8*, 1339.
9. Adrio, J.; Carretero, J. C.; García Ruano, J. L.; Martín Cabrejas, L. M. *Tetrahedron: Asymmetry* **1997**, *8*, 1623.
10. Carretero, J. C.; García Ruano, J. L.; Martín Cabrejas, L. M. *Tetrahedron: Asymmetry* **1997**, *8*, 2215.
11. Other related systems had been previously reported: (a) Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Tetrahedron*

Lett. **1985**, *26*, 6205. (b). Chau, T.-Y.; Lin, H.-C.; Hu, W. *Synth. Commun.* **1996**, *26*, 1867.

12. Alonso, I.; Carretero, J. C.; García Ruano, J. L. *J. Org. Chem.* **1993**, *58*, 3231.
13. Alonso, I.; Carretero, J. C.; García Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 1499.
14. Carretero, J. C.; García Ruano, J. L.; Martín Cabrejas, L. M. *Tetrahedron Lett.* **1994**, *35*, 5895.
15. Carretero, J. C.; García Ruano, J. L.; Martín Cabrejas, L. M. *Tetrahedron* **1995**, *51*, 8323.
16. García Ruano, J. L.; Esteban Gamboa, A.; Martín Castro, A. M.; Rodríguez, J. H.; López-Solera, M. I. *J. Org. Chem.* **1998**, *63*, 3324.
17. García Ruano, J. L.; Alemparte, C.; Martín Castro, A. M.; Adams, H.; Rodríguez Ramos, J. H. *J. Org. Chem.* **2000**, *65*, 7938.
18. Koizumi, T.; Hakamada, I.; Yoshi, E. *Tetrahedron Lett.* **1984**, *25*, 87.
19. Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* **1984**, *25*, 1727.
20. Brimble, M. A.; Davis, B. R. *Tetrahedron* **1985**, *41*, 4965.
21. Proust, S. M.; Ridley, D. D. *Aust. J. Chem.* **1984**, *37*, 1677.
22. Yamakoshi, Y. N.; Ge, W.-Y.; Sugita, J.; Okayama, K.; Takahashi, T.; Koizumi, T. *Heterocycles* **1996**, *42*, 129.
23. Hiroi, K.; Umemura, M. *Tetrahedron* **1993**, *49*, 1831.
24. Toscano, R. A.; Hernández-Ortega, S.; Ortiz, B.; Sánchez-Obregón, R.; Walls, F.; Yuste, F. *Acta Crystallogr.* **2001**, *C57*, 1313.
25. Arce, E.; Carreño, M. C.; Cid, M. B.; García Ruano, J. L. *Tetrahedron: Asymmetry* **1995**, *6*, 1757.
26. García Ruano, J. L.; Esteban Gamboa, A.; González Gutiérrez, L.; Martín Castro, A. M.; Rodríguez, J. H.; Yuste, F. *Org. Lett.* **2000**, *2*, 733.
27. Pirkle, W. H.; Hoover, D. J. *Topics in Stereochemistry*; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley-Interscience: New York, 1982; Vol. 13, p. 263.
28. Mannschreck, A.; Jonas, V.; Kolb, B. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 909.
29. Rayner, D. R.; Gordon, A. J.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4854.