

The sulfinyl group as a chiral inductor in asymmetric Diels–Alder reactions

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Abstract

The role of the sulfinyl group on the reactivity and the selectivity of vinylsulfoxides as dienophiles is analyzed from the results obtained in the reactions of some optically pure sulfinylesters and sulfinylquinones with cyclic and acyclic dienes. The effect of high pressures on these cycloadditions has also been evaluated.

The sulfinyl group had scarcely been a subject of interest in conventional Diels–Alder reactions due to its low ability as an activating group of dienophiles. Nevertheless, the intrinsic chirality of the group, its configurational stability under very different conditions and the facility to be introduced in organic molecules in an optically pure form, draw the attention of the researchers working in different fields of asymmetric synthesis. From then on, its ability to control the π -facial selectivity has provided the impetus for the use of optically pure α,β -unsaturated sulfoxides as dienophiles in asymmetric Diels–Alder reactions.

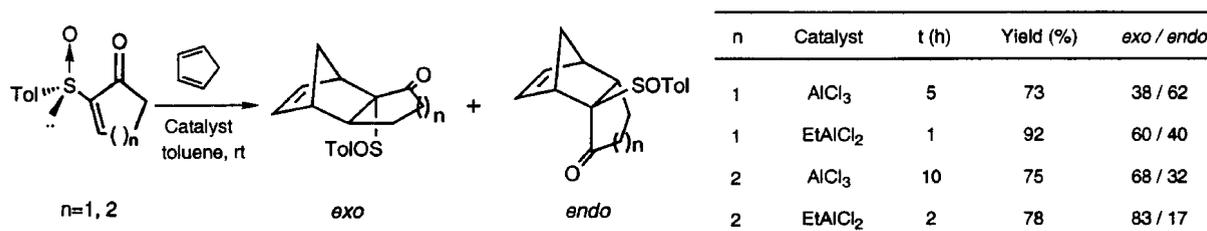
The first report concerning the use of optically pure vinylsulfoxides as dienophiles described the reaction of the (S)-vinyl 2-*p*-tolylsulfoxide with cyclopentadiene.¹ The results revealed that the sulfinyl group has a moderate *endo*-orientating character (the *endo/exo* ratio was 64:36) and a poor ability to control the π -facial selectivity, besides its well-known low influence on the reactivity (115° C in a sealed tube were required). This suggested that the introduction of a second electron-withdrawing group at the double bond that increased its dienophilic reactivity and restricted the conformational mobility around the C–S bond would be essential to take advantage of the properties of the sulfinyl group as a chiral inductor, as well as to improve them. During the last few years, some studies concerning asymmetric Diels–Alder reactions of vinylsulfoxides containing ketone² and nitro groups³ have been reported, but the pioneering and most complete studies are related to the use of the sulfinylacrylates from the Koizumi,⁴ Maignan,⁵ and De Lucchi⁶ groups.

When we started our research on the use of enantiomerically pure vinylsulfoxides in asymmetric Diels–Alder reactions in 1988, it had been postulated that the stereochemical course of these reactions was controlled on steric grounds, and thus the favored approach of the diene would take place from the less hindered face of the vinylsulfoxides, which is the one displaying the lone electron pair at the sulfur. Accordingly, the conformational preferences of the dienophiles around the C–S bond were postulated as the main factor controlling the π -facial selectivity, the electrostatic repulsion between the sulfinyl oxygen and the ester group being the main factor invoked to explain them. Moreover, the use of ZnCl₂ as the catalyst in reactions of α -sulfinylacrylates was known to invert the π -facial selectivity, due to the formation of chelated species with the lone electron pair at sulfur oriented towards the opposite face to that of the non-chelated ones.

The main problems to be solved were related to the rather moderate reactivity of the sulfinyldienophiles (despite the second electron-withdrawing group at the double bond the majority of the

reported Diels-Alder reactions were related only with the use of cyclopentadiene or other cyclic dienes) and to the low *endo-exo* selectivity of their cycloadditions. These facts strongly limited the synthetic usefulness of vinylsulfoxides as dienophiles in asymmetric synthesis. The search of new sulfinyldienophiles and/or catalysts that were able to overcome these problems, retaining and even increasing the high π -facial selectivity, were the main challenge of our research.

Our first contribution concerned the use of 2-sulfinylcycloalkenones as dienophiles.⁷ These substrates were studied to check whether the presumably higher reactivity and *endo*-selectivity of the enones with respect to the acrylates was enough to increase the interest of the cycloadditions. However, our results suggested that this was not the case. The reactivity of the sulfinylcycloalkenones was even lower than that exhibited by some 2-sulfinylacrylates previously reported, and required the use of EtAlCl₂ or AlCl₃ as catalysts in their reactions with cyclopentadiene (low conversions were obtained with weaker Lewis acids as catalysts). Moreover, the *endo/exo* selectivity of these reactions was also low, probably due to the competence between sulfinyl and carbonyl groups, both exhibiting an *endo* orientating character. The most outstanding fact of these reactions is their complete π -facial selectivity, yielding only the *endo* and *exo* adducts resulting from the approach of the diene on the face displaying the lone electron pair at sulfur in the chelated species formed from dienophile and catalyst. The predominance of the *exo* adducts, which was higher for sulfinyl cyclohexenone, should be related to the cyclic structure of the enone (Scheme 1).



Scheme 1

Recently we have taken advantage of the high π -facial selectivity of these dienophiles to synthesize the steroid skeleton in a single step, by reaction of 2-*p*-tolylsulfinyl cyclopentenone with the Dane's diene.⁸ As in the previous case, EtAlCl₂ was the most efficient catalyst and the reaction took place with complete *endo*-selectivity whereas the π -facial selectivity depended on the reaction conditions.

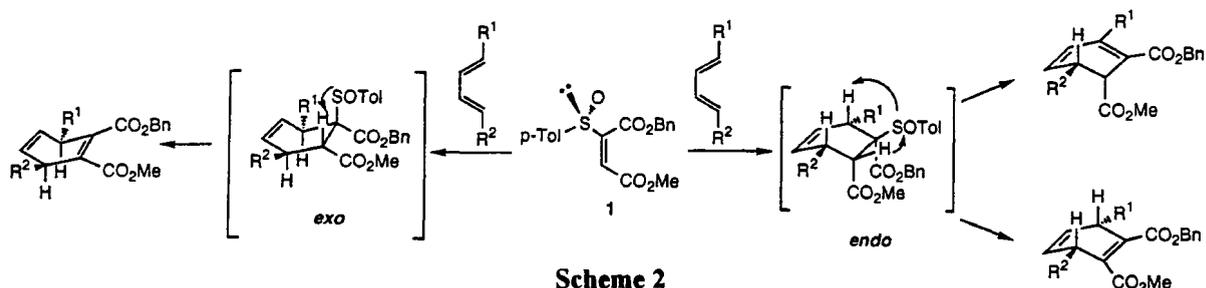
From these and other reported results it was evident that both reactivity and *endo*-selectivity of vinylsulfoxides containing only one additional electron-withdrawing group at the double bond are rather moderate. In order to overcome these important limitations and to obtain dienophiles able to react with acyclic dienes in a high *endo*-selective manner, we decided to study vinylsulfoxides containing two additional activating groups in *cis* arrangement, like 2-sulfinylmaleates and 2-sulfinylquinones.

We have studied different sulfinyl maleates,⁹ 1-benzyl 4-methyl (*S*)-2-*p*-tolylsulfinyl maleate **1** being the most efficient.^{10,11} Its reactions with cyclopentadiene yielded mixtures of three adducts (the two possible *endo* and only one *exo*) whose relative ratios were dependent on the reaction conditions. In the absence of catalyst, its complete evolution required 10 hours at room temperature. These conditions are similar to those used by Koizumi in the reactions of cyclopentadiene with 2-*p*-tolylsulfinyl acrylates.^{4a} Furthermore, the *endo/exo* selectivity is also similar for both dienophiles, thus indicating that the second ester group does not mean any significant improvement in the characteristics of the dienophile. Fortunately, we found that the use of TiCl₄ as a catalyst substantially increased both the reactivity (dienophile required only 2 hours at -78°C to be transformed into the mixture of adducts) and the *endo*-selectivity, while the π -facial selectivity remained high.^{10,11} Other catalysts were less efficient (Eu(fod)₃ induced the best *endo*-selectivity but the worst *endo/exo* ratio, while ZnBr₂, which combined the highest *endo*-selectivity with a quite high π -facial selectivity, meant the poorest improvement in the reactivity¹¹).

The treatment of **1** with acyclic dienes gave satisfactory results only in the presence of Eu(fod)₃ or TiCl₄. Additionally, the resulting sulfinyl cyclohexenes are very unstable, undergoing spontaneous sulfinyl elimination at room temperature to give the corresponding cyclohexadienes. The reactions with butadiene

and 2-substituted dienes only yielded optically pure 1,3-cyclohexadienes, thus suggesting that both regioselectivity and π -facial selectivity of the cycloadditions are complete, as well as the regioselectivity of the sulfinyl elimination.

In these cases, the reactivity, much higher under TiCl_4 catalysis, is the only difference between both catalysts. This situation changed in reactions of **1** with 1-substituted dienes because of the problem of the *endo/exo* selectivity. Reactions catalyzed by $\text{Eu}(\text{fod})_3$ yielded a mixture of *endo* and *exo* adducts. As expected from the *syn* character of the pyrolytic sulfinyl elimination, the *endo* adducts evolved into a mixture of 1,3- and 1,4-cyclohexadienes, whereas the enantiomers of the latter were the only products obtained from the *exo* adducts. Accordingly, the optical purity of the 1,4-cyclohexadienes is only moderate. The reactions catalyzed by TiCl_4 only yielded one *endo*-adduct, which was transformed into a mixture of 1,3- and 1,4-cyclohexadienes, both of them optically pure.



Reactions of **1** with 1-vinylcycloalkenes under TiCl_4 catalysis afforded mixtures of the two possible sulfinyl elimination products in high optical purity. The regioselectivity of the elimination depends on the size of the second ring, the formation of the 1,4-cyclohexadiene derivatives for seven or higher membered rings being almost exclusive.¹²

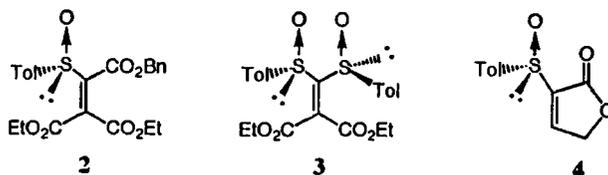
As summary, we can conclude that the reactions of sulfinyl maleate **1** with acyclic dienes carried out under TiCl_4 catalysis take place in very mild conditions with a complete control of the regioselectivity, *endo-exo* selectivity and π -facial selectivity. All these advantages must be attributed to the catalyst because without it the behavior of the sulfinyl maleates was similar to that of the sulfinyl acrylates. It suggested that the behavior of the latter under TiCl_4 catalysis should be investigated. We have synthesized benzyl 2-*p*-tolylsulfinyl acrylate and studied its reactions with different dienes.¹³ With cyclopentadiene the *endo*-selectivity was moderate but the reaction took place in only half an hour at -78°C , indicating a substantial increase of the reactivity.¹⁴ The *endo*-selectivity increased with 2-methylfuran and became complete with acyclic dienes like Dane's diene.

From a synthetic point of view, the reactions of the maleates have two main problems which restricts its synthetic usefulness: the low regioselectivity of the sulfinyl elimination in reactions with 1-substituted dienes, and the fact that TiCl_4 cannot be used with oxygenated dienes, which are decomposed by this catalyst. We have studied the behavior of sulfinyl trialkoxycarbonyl ethene **2** to check whether the presence of the third ester group was able to overcome both problems.¹⁵ The obtained results indicate that the reactivity was very similar to that of the maleates (TiCl_4 had to be used as catalyst). Regioselectivity and π -facial selectivity were very high with cyclic and acyclic dienes, regardless the catalyst used. Reactions with cyclopentadiene exhibited a moderate (with $\text{Eu}(\text{fod})_3$ or ZnBr_2 catalysis) or high (with TiCl_4) *exo*-selectivity, which disappeared with acyclic dienes. Accordingly, the optical purity of the 1,3-cyclohexadienes obtained by spontaneous pyrolysis of the formed adducts was very low. The comparison between these results and those obtained from maleates shows that π -facial and the *endo/exo* selectivities are the opposite for each dienophile. It was explained on the basis of the conformational preferences around the C-S bond.¹⁵

At that moment, we decided to investigate the effect of the high pressures on the dienophilic behavior of different vinylsulfoxides. The reaction of **2** with piperilene, which at normal pressure only progressed under TiCl_4 catalysis, could be performed under thermal conditions or even better under ZnBr_2 or $\text{Eu}(\text{fod})_3$ catalysis. Nevertheless, its effect on the *endo* selectivity is scarcely significant and thus the optical purity of the adducts remained very low.¹⁵ These results suggested that the interest of the high pressure must be focused on the study of dienophiles of very low reactivity.

The reaction of piperilene with (R,R)-1,1-bis-*p*-tolylsulfinyl 2,2-diethoxycarbonyl ethylene, **3**, at 13 Kbar (it did not work at normal pressure) gave high yields of only one optically pure cyclohexadiene,¹³ which demonstrated that both regioselectivity and π -facial selectivity of the cycloaddition are very high, the first being controlled by the gem-diester group. Other acyclic dienes like vinylcyclohexene and the Dane's diene gave similar results, whereas the π -facial selectivity slightly decreased in the reactions with cyclopentadiene at 13 Kbar (a 93:7 mixture of two diastereoisomers resulting from the attack of the diene on the two diastereotopic faces of the dienophile was obtained).

We have also investigated the cycloadditions of 2-*p*-tolylsulfinyl 2-butenolide, **4**, under high pressures.¹³ This dienophile exhibits a lower reactivity than that of 2-sulfinylacrylates and it does not react with cyclopentadiene at reflux. Additionally it is decomposed by Lewis acids, which precluded their use as catalysts. Therefore, Diels-Alder reactions on this dienophile would be possible only under high pressures. At 13 Kbar, cyclopentadiene afforded a mixture of the four possible diastereoisomers. Both π -facial and *endo/exo* selectivities are moderate. With piperilene and vinylcyclohexene the adducts evolved into mixtures of the sulfinyl elimination products, whose optical purity has not been yet evaluated. With the Dane's diene the sulfinyl adduct could be isolated as the only reaction product, suggesting that this reaction takes place with a complete control of the regio-, *endo*-, and π -facial selectivities.



Scheme 3

The second group of dienophiles whose study was developed in our group simultaneously to that of the sulfinylesters is that of the 2-*p*-tolylsulfinyl quinones. Our interest in these substrates is related to their use in asymmetric synthesis of anthracyclonones, which is the final synthetic objective of this research. We will consider herein only the methodological aspects concerning the role of the sulfinyl group in the course of the asymmetric Diels-Alder reactions on sulfinyl quinones.

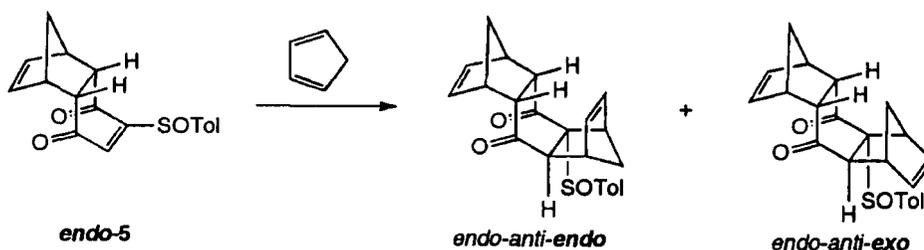
Different approaches were used to synthesize optically pure 2-*p*-tolylsulfinyl benzoquinone. The best involves the sulfonylation of the hydroquinone dimethylether or its brominated derivative, followed by C.A.N. oxidation into the sulfinylquinones.¹⁶ The ee of the resulting compound is higher than 97%. A similar route was used to synthesize 3-ethyl and 3-chloro 2-*p*-tolylsulfinyl-*p*-benzoquinones¹⁷ and sulfinyl naphthoquinones with methoxy or hydroxy substituents^{18,19} in different positions. During the oxidation step the ring with higher electron density is the most easily oxidized.

Concerning their cycloaddition reactions, the first question to be clarified was related to the chemoselectivity of the diene attack on sulfinyl *p*-benzoquinones²⁰ with two dienophilic double bonds. The reaction of cyclic dienes with 2-*p*-tolylsulfinyl *p*-benzoquinone yielded the adducts resulting from the attack of diene on the unsubstituted C₅-C₆ double bond, whereas the acyclic dienes reacted on the C₂-C₃ double bond. In this case, the adducts could not be isolated and evolved into the sulfinyl elimination products, which in the case of the oxygenated dienes suffered further spontaneous aromatization (this is the main synthetic limitation of the use of sulfinylquinones as dienophiles). All these reactions took place in very mild conditions in the absence of catalysts, which demonstrates that the reactivity of these dienophiles is substantially higher than that of the sulfinyl esters. The different chemoselectivity of the cyclic and acyclic dienes has been explained by assuming an activating effect of the sulfinyl group due to its electron-withdrawing power, determining that acyclic dienes only react on C₂-C₃. With cyclic dienes this effect must be overridden by the steric interactions between the methylenes bridge and the sulfinyl moiety directing the cycloaddition on C₅-C₆.

Starting from 3-substituted 2-*p*-tolylsulfinyl benzoquinones,¹⁷ cyclic and acyclic dienes reacted on the unsubstituted C₅-C₆ double bond. The interactions between the substituent at C-3 and the sulfinyl group must determine the lone electron pair at sulfur to adopt the *s-cis* arrangement and thus the approach of the

diene from the diastereotopic faces at C₂-C₃ will be respectively hindered by sulfinyl oxygen and tolyl group.

Concerning the regioselectivity, the sulfinyl group is very efficient to control it. This conclusion was reached from the study of the reactions of sulfinyl naphthoquinones with 1-methoxy cyclohexadiene²¹ and piperilene.¹³ With respect to the stereoselectivity we must consider two different aspects, related to the *endo-exo* and the π -facial selectivities. First of all, the *endo* orientating character of the quinonic system is clearly higher than that of the sulfinyl group, and thus the stereochemistry of the adducts with cyclopentadiene was *endo*, regardless the dienophilic double bond where the cycloaddition had taken place. The only case where the *exo*-adducts has been characterized was in the reactions of the *endo* monoadducts **5** with cyclopentadiene,¹³ which yields mixtures of the bisadducts where the stereochemistry of the second cycloaddition is *endo* and *exo*, respectively (Scheme 4). The planarity of the quinonic systems must be responsible of their strong *endo* orientating character. The absence of planarity in **5** as well as that of the ester groups at sulfinylmaleates and sulfinyl triester would explain the formation of mixtures of *endo* and *exo* adducts in their reactions with cyclopentadiene.



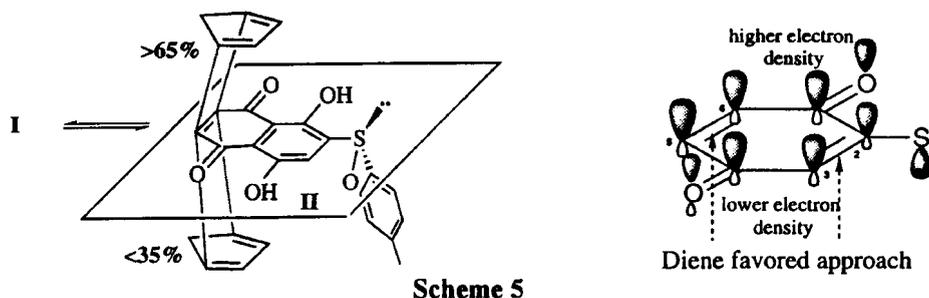
Scheme 4

Three main factors must be considered to understand the π -facial selectivity of these reactions: the dienophilic double bond where the cycloaddition was taking place, the cyclic or acyclic structure of the diene and the reaction conditions, mainly solvent, temperature and catalyst. The π -facial selectivity of cycloadditions with cyclic dienes on C₂-C₃ has been studied on sulfinyl naphthoquinones²¹ and it can be explained by assuming a steric approach control, similar to that proposed for other vinylsulfoxides.

When the reactions took place on the C₅-C₆ double bond of 2-sulfinyl-*p*-benzoquinone,²⁰ they surprisingly evolved with a significant π -facial selectivity despite the long distance between the dienophilic bond and the chiral center. Both reactivity and π -facial selectivity increased with the polarity of the solvent used in the reaction,¹³ which presumably must increase the population of the most polar rotamer around the C-S bond. The catalysts have also a large influence on the π -facial selectivity. In the presence of Eu(fod)₃ the selectivity is even higher than in the most polar solvent. The use of BF₃·OEt₂ causes the complete inversion of the selectivity.²⁰ Similar influence but with a much lower selectivity was observed under ZnBr₂ catalysis.¹³

These results were initially explained invoking a steric approach control,^{20,21} but the long distance between dienophilic C₅-C₆ double bond and the substituents around the sulfur suggested that the steric hindrance would not be the main factor determining the high π -facial selectivity. This assumption was reinforced from the fact that reactions of cyclopentadiene with tautomer **II** of the sulfinyl naphthazarin also evolved with significant π -facial selectivity.¹³ In this substrate the steric effects cannot be invoked due to the long distance between the dienophilic double bond and the sulfur atom (Scheme 5).

We propose that stereoelectronic factors independent of the distance could be the main responsible of the stereochemical behavior. The electronic repulsion between the lone electron pair at sulfur and the π -cloud of the quinonic system would be minimized by increasing the electronic density of the face opposite to that displaying the lone electron pair, which provokes disymmetrization of the electron π -cloud (less marked when the π -extended system is larger). As the favored approach of the diene must take place from the face of the dienophile with lower electron density, the orientation of the lone electron pair at sulfur will be able to control the π -facial selectivity (Scheme 8). In order to obtain evidences about this qualitative assumption, we are currently involved in theoretical calculations concerning the interactions between the lone electron pair at sulfur with the HOMO and mainly with the LUMO orbitals at the extended quinonic systems.



In summary, all these studies have demonstrated that the sulfinyl group has a small effect on the reactivity, which can be overridden by using the appropriated catalyst and/or additional activating groups like esters or carbonyls. On the other hand, the sulfinyl group is very efficient in the control of both the regioselectivity and the π -facial selectivity of the cycloadditions on activated vinylsulfoxides. All these characteristics confer to the sulfinyl group a high ability as a chiral inductor.

Acknowledgments: We thank DGICYT (Grant PB92-0161 and PB93-0257) for financial support

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