

## Asymmetric 1,3-dipolar reactions of cyclic vinyl *p*-tolyl sulfilimines with diazoalkanes

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**Dedicated to Professor José Elguero on the occasion of his 70<sup>th</sup> birthday and Professor Pedro Molina on the occasion of his 60<sup>th</sup> birthday**  
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### Abstract

1,3-Dipolar reactions of vinyl *p*-tolyl sulfilimines **1** and **2** with diazoethane afforded mixtures of adducts with almost complete  $\pi$ -facial- selectivity and a high *exo/endo*- selectivity, under smooth conditions. The *anti*- approach with respect to the tolyl group, and the *exo*- arrangement of the dipole are clearly favored on steric grounds. Reactions with diazomethane are slower and less stereoselective.

**Keywords:** Asymmetric 1,3-dipolar additions, cyclic vinyl sulfilimines, diazoalkanes, chiral  $\Delta^1$ -pyrazolines

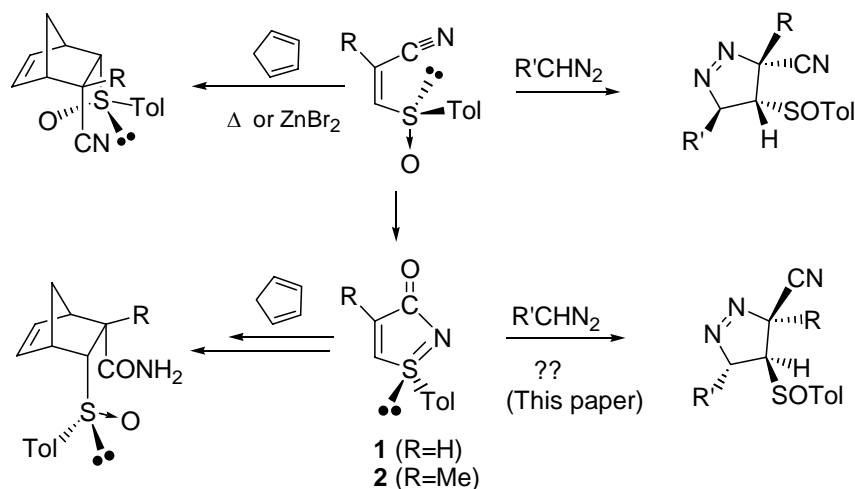
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### Introduction

Vinyl sulfoxides have been shown to be efficient chiral dienophiles<sup>1</sup> owing to the ability of the sulfinyl group to differentiate the diastereotopic faces of the double bond. In order to increase the reactivity as well as the  $\pi$ -facial- and *endo*- selectivities, the presence is required at the double bond of other electron-withdrawing groups restricting the conformational equilibrium around the C–S bond. In the course of our studies on the behavior of differently substituted activated vinyl sulfoxides as chiral dienophiles in asymmetric Diels-Alder reactions,<sup>1a,2</sup> we have demonstrated that (*Z*)-3-*p*-tolylsulfinylacrylonitriles exhibit high reactivity, a complete  $\pi$ -facial selectivity and a very high *endo*-selectivity<sup>3,4</sup> (Scheme 1). These features transform 3-sulfinylacrylonitriles into some of the most efficient sulfinyl-dienophiles so far reported. We found that the transformation of (*Z*)-3-*p*-tolylsulfinylacrylonitriles into the cyclic vinyl- *p*-tolylsulfilimines (**1** and **2**) allowed

us to invert the  $\pi$ -facial selectivity of the Diels-Alder reactions with cyclopentadienes<sup>5</sup> and others dienes<sup>6</sup> (Scheme 1).

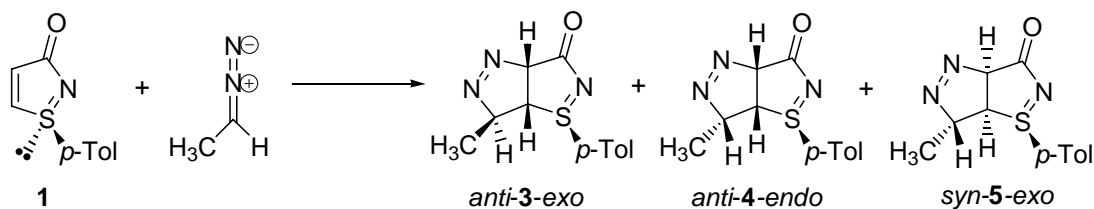
We have recently demonstrated that (*Z*)-3-*p*-tolylsulfinylacrylonitriles are also excellent dipolarophiles in their asymmetric reactions with diazoalkanes,<sup>7</sup> and their adducts can easily be converted into cyclopropanes.<sup>8</sup> On this basis, we decided to study the dipolarophilic behavior of cyclic vinyl *p*-tolyl sulfilimines to check whether they are also complementary to sulfinylacrylonitriles when they are confronted with diazoalkanes. The results obtained in the reactions of the sulfilimines **1** and **2** (Scheme 1) with diazoethane and diazomethane are presented in this paper.



Scheme 1

## Results and Discussion

Compounds **1** and **2** were prepared according to the previously reported procedure.<sup>5</sup> The reaction of (*R*)-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**1**) with diazoethane proceeded under quite smooth conditions (<20 °C) in short or moderate reaction times (<90 min). The results are collected in Table 1.



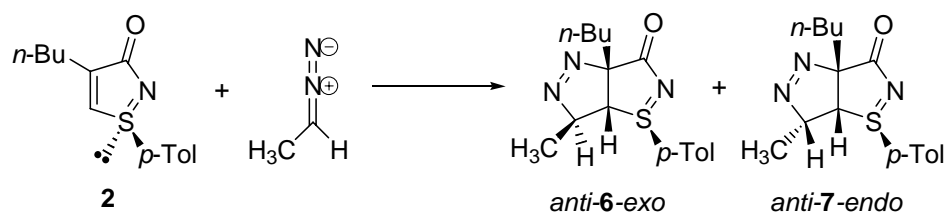
The reaction afforded mixtures of three cycloadducts, **3–5**, two of them (**3** and **4**) obtained as the major products regardless the used conditions. The use of CH<sub>2</sub>Cl<sub>2</sub> as the solvent (entries 2-5)

meant an improvement in the *endo/exo* and  $\pi$ -facial selectivities, which were not substantially modified by any change in the temperature. Compounds **3-5** could not be isolated diastereomerically pure, either by crystallization or by chromatography. Therefore, they were characterized from the spectroscopic data of diastereomeric mixtures of the cycloadducts.<sup>9</sup>

Reactions of (*R*)-4-*n*-butyl-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**2**)<sup>5</sup> with diazoethane, performed under similar experimental conditions, gave the results collected in Table 2.

**Table 1.** Results of the reaction of (*R*)-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**1**) with diazoethane

Entry	Solvent	<i>T</i> (°C)	<i>t</i> (min)	<i>anti</i> -3- <i>exo</i>	<i>anti</i> -4- <i>endo</i>	<i>syn</i> -5- <i>exo</i>
<b>1</b>	Et <sub>2</sub> O, EtOH	0	15	57	33	12
<b>2</b>	CH <sub>2</sub> Cl <sub>2</sub>	20	20	78	22	-
<b>3</b>	CH <sub>2</sub> Cl <sub>2</sub>	0	30	71	23	6
<b>4</b>	CH <sub>2</sub> Cl <sub>2</sub>	-20	50	75	19	6
<b>5</b>	CH <sub>2</sub> Cl <sub>2</sub>	-40	90	76	20	4



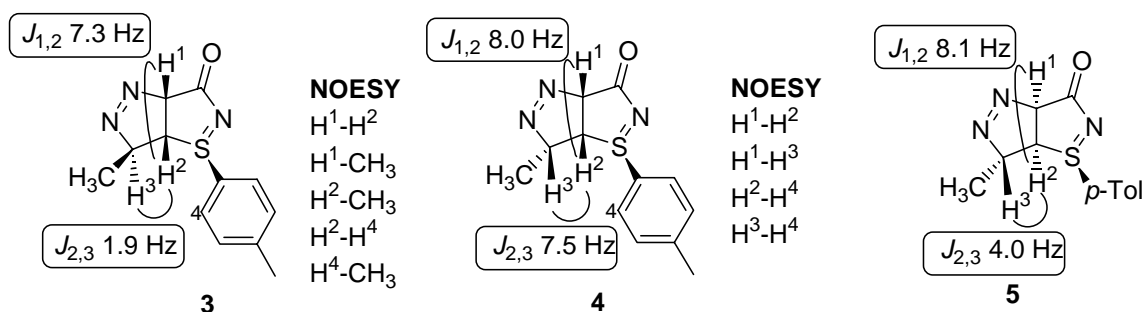
**Table 2.** Results of the 1,3-dipolar cycloadditions of (*R*)-4-*n*-butyl-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**2**) with diazoethane

Entry	Solvent	<i>T</i> (°C)	<i>t</i> (days)	<i>anti</i> -6- <i>exo</i>	<i>anti</i> -7- <i>endo</i>
<b>1</b>	Et <sub>2</sub> O, EtOH	0	3	75	25
<b>2</b>	CH <sub>2</sub> Cl <sub>2</sub>	20	1	81	19
<b>3</b>	CH <sub>2</sub> Cl <sub>2</sub>	0	2	84	16
<b>4</b>	CH <sub>2</sub> Cl <sub>2</sub>	-20	4	87	13
<b>5</b>	CH <sub>2</sub> Cl <sub>2</sub>	-40	6	88	12

As expected, reactions of **2** with diazoethane required longer reaction times to reach completion than those needed for the sulfilimine **1**. The process afforded only two adducts, *anti*-6-*exo*- and *anti*-7-*endo*-, with complete control of the  $\pi$ -facial selectivity and a high *exo*-selectivity. The latter was improved when CH<sub>2</sub>Cl<sub>2</sub> was used as the solvent for the reaction (compare entries 1 and 3). Additionally, a slight increase in the proportion of *exo*- adduct was detected when the temperature was lower (entries 2–5).

The thermal instability of the adducts hindered their isolation; hence, these compounds were also characterized from diastereomeric mixtures of **6** and **7**. As in the case of compounds **3-5**, the stereochemical assignment was made by spectroscopic methods.

$^1\text{H-NMR}$  and HMQC experiments proved the complete control of the regioselectivity of the cycloaddition of **1** with diazoethane. The relative configuration of the chiral centers in cycloadducts **3–5** was established by NOESY experiments, and also from the values of their coupling constants (Figure 1).



**Figure 1**

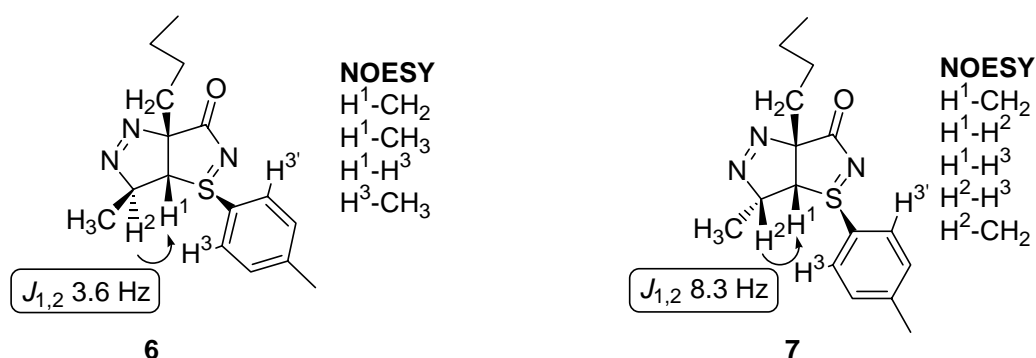
Bearing in mind the fact that the *S*- configuration at sulfur must not be affected during the cycloaddition, the NOESY effect observed between hydrogen atoms at the *ortho*- position at the aromatic ring ( $\text{H-4}$  and  $\text{H-4}'$ ) and the hydrogen  $\text{H-2}$ , for adducts **3** and **4**, evidence a *syn*-arrangement of both substituents, which accounts for the *R*- absolute configuration at the chiral carbon bonded to  $\text{H-2}$ .

The values of  $J_{1,2}$  (7.3 Hz for **3**, and 8.0 Hz for **4**) show a *syn*- arrangement of  $\text{H-1}$  and  $\text{H-2}$ , both for **3** and for **4**, in agreement with the concerted mechanism of these cycloadditions. The absolute configurations at the chiral centers derived from diazoethane (*R*- for **3** and *S*- for **4**) were initially established from the coupling constant values  $J_{2,3}$  for each adduct. The value of 1.9 Hz observed for **3** is evidence of an *anti*- arrangement for  $\text{H-2}$  and  $\text{H-3}$  in adduct **3**, whereas the value of 7.5 Hz for **4** indicates that both hydrogen atoms adopt a *syn*- arrangement. The NOESY effect detected between  $\text{H-2}$  and  $\text{CH}_3$  for adduct **3**, and between  $\text{H-2}$  and  $\text{H-3}$  for **4**, lead to the same conclusion. From all these data, the *anti-exo* stereochemistry for the major adduct **3** and the *anti-endo* stereochemistry for adduct **4** could be established.<sup>10</sup>

The configurational assignment of the minor adduct, **5**, was only tentative. The only available data are related to the coupling constants  $J_{1,2}$  (8.1 Hz) and  $J_{2,3}$  (4.0 Hz). The former value, indicative of a *cis*- arrangement of the hydrogen atoms, is a consequence of the cyclic structure of the dipolarophile and of the concerted character of the reaction. The latter value suggests a *trans* arrangement of  $\text{H-2}$  and  $\text{H-3}$ . As the two major cycloadducts **3** and **4** exhibit an *anti*-stereochemistry, compound **5** must be *syn*-. The observed value for  $J_{2,3}$  (4.0 Hz) suggests its *exo* nature. Unfortunately, the small proportion of **5** in the obtained diastereomeric mixtures did not allow a NOESY experiment, which would have confirmed this tentative assignment unequivocally.

As we have already seen (see Table 2), the 1,3-dipolar cycloaddition reaction of vinyl sulfilimine **2** with diazoethane afforded a mixture of only two adducts **6** and **7**, with **6** being

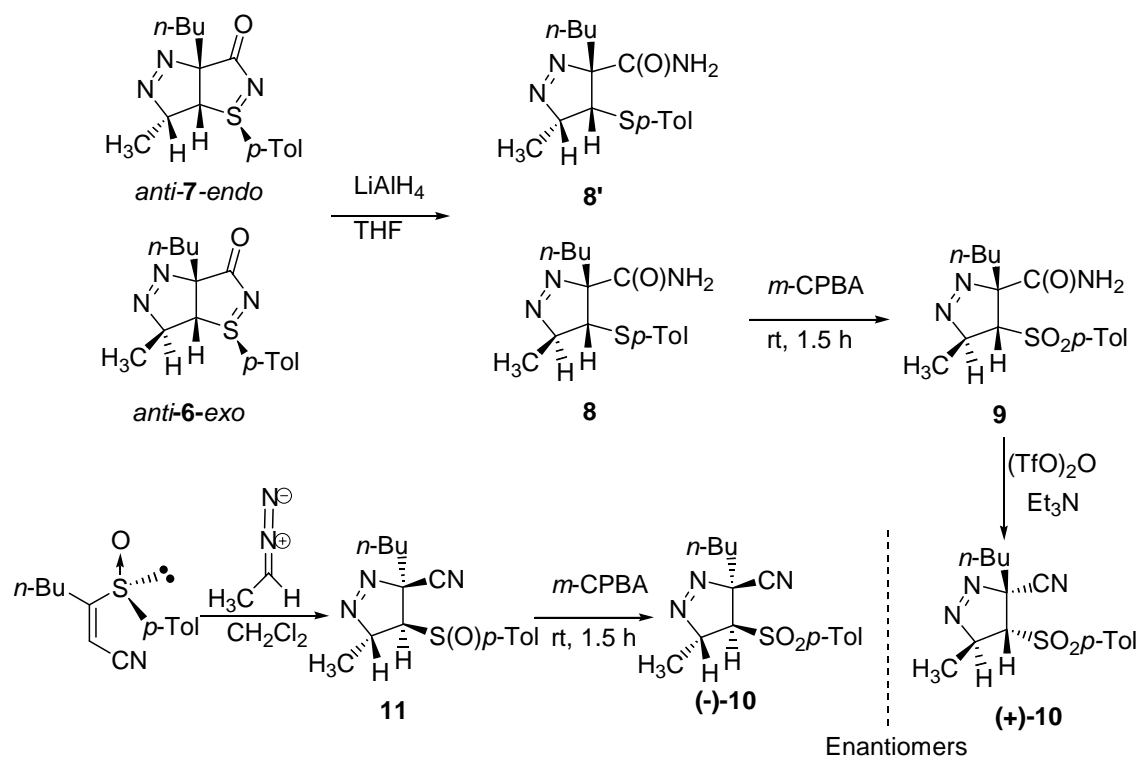
clearly predominant in the reaction mixtures under all the conditions tested. The regioselectivity (confirmed by  $^1\text{H-NMR}$  and HMQC experiments) and the relative configuration in the stereogenic carbon atoms in the adducts (deduced from NOESY experiments, Figure 2) was determined as in the previous case. This relative configuration becomes the absolute configuration if we admit that the *R*- configuration at the chiral sulfur does not change during the reaction.



**Figure 2**

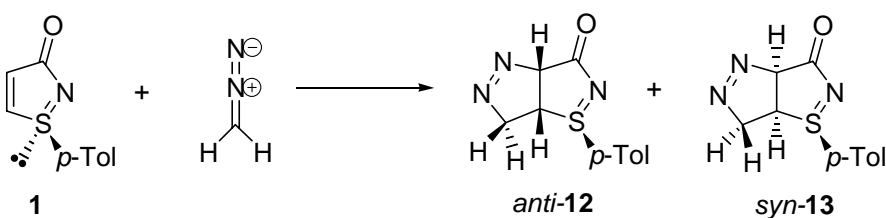
As was the case for **3** and **4**, the value of the coupling constants for H-1 and H-2 allowed us to determine the configuration at the chiral center derived from diazoethane. In the major cycloadduct **6**, the constant  $J_{1,2}$  is 3.6 Hz, which indicates a *trans*- arrangement and, therefore, an *exo*- stereochemistry. Similarly, the *endo*- stereochemistry for the minor adduct **7** was deduced from the value of 8.3 Hz for the coupling constant  $J_{1,2}$ , indicative of a *cis*- arrangement of H-1 and H-2.

The absolute configuration of **6** was finally corroborated by chemical correlation with compound **11** (obtained by reaction of (*Z*)-3-*p*-tolylsulfinyl-2-*n*-butylacrylonitrile with diazoethane),<sup>7</sup> whose configuration was already known by X-ray diffraction. Thus, reduction of the sulfilimine functionality by treatment of a mixture of **6** and **7** with  $\text{LiAlH}_4$  afforded an epimeric mixture of sulfenylcarboxamides, **8** and **8'**. Only diastereomerically pure **8** could be isolated by chromatography of the crude reaction mixture (Scheme 2). It was oxidized into sulfone **9** and then dehydrated to the sulfonylcyanopyrazoline **10**. The spectroscopic properties ( $^1\text{H}$ - and  $^{13}\text{C}$ - NMR) of **10** were coincident with those of the compound prepared by oxidation of **11** (Scheme 2), but the values of the specific optical rotation for both compounds **10** derived from *anti*-**6-exo** and **11**, respectively, exhibited the opposite sign, (+)-**10** and (-)-**10**. This led to the conclusion that they are enantiomers and, therefore, resulting from the approach of the diazoethane to the dipolarophile with opposite  $\pi$ -facial selectivities, in agreement with the results from Diels–Alder cycloadditions for both types of substrates.



## Scheme 2

In Table 3 are collected the most relevant results obtained in the 1,3-dipolar cycloaddition reactions of (*R*)-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**1**) with diazomethane under different experimental conditions. Under similar, and even stronger, conditions compound **2** does not react with diazomethane.

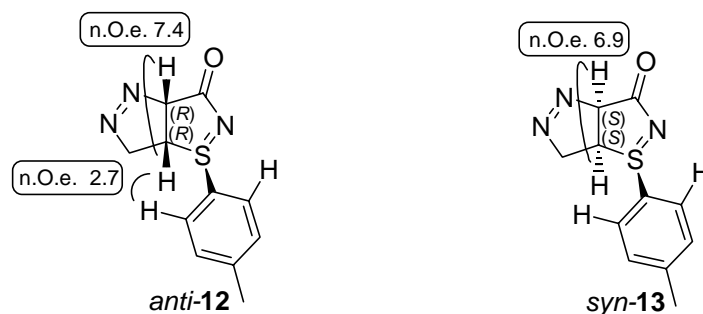


**Table 3.** Results of the 1,3-dipolar cycloaddition of (*R*)-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**1**) with diazomethane

Entry	Solvent	<i>T</i> (°C)	<i>t</i> (min)	<i>Anti-12</i>	<i>Syn-13</i>
<b>1</b>	Et <sub>2</sub> O, MeOH	0	30	50	50
<b>2</b>	CH <sub>2</sub> Cl <sub>2</sub>	20	10	90	10
<b>3</b>	CH <sub>2</sub> Cl <sub>2</sub>	0	20	86	14
<b>4</b>	CH <sub>2</sub> Cl <sub>2</sub>	-20	120	84	16
<b>5</b>	CH <sub>2</sub> Cl <sub>2</sub>	-40	240	81	19

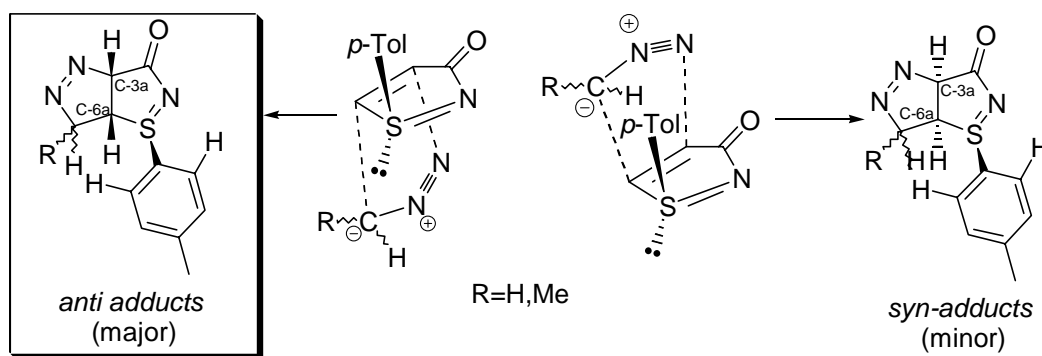
The reactions of **1** with this dipole were complete under mild conditions in short or moderate reaction times to yield two diastereomeric cycloadducts, *anti*-**12** and *syn*-**13**, resulting from both  $\pi$ -facial approaches of diazomethane to the dipolarophile. As was the case for the reactions with diazoethane (Table 1), the best stereoselectivity was observed using  $\text{CH}_2\text{Cl}_2$  as the solvent (entries 2–5). As expected, the reactivity of **1** decreased as the temperature was lower. Surprisingly, the  $\pi$ -facial selectivity also decreased with the reaction temperature (compare entries 2–5).

All attempts failed to isolate diastereomerically pure **12** and **13**, either by crystallization or by chromatography, possibly owing to the instability of these compounds. Therefore, their characterization was made from the spectroscopic parameters of freshly prepared cycloadduct mixtures. Once again, NMR experiments (COSY and HMQC) allowed us to determine that 1,3-dipolar cycloadditions of vinyl sulfilimine **1** proceed with complete control of the regioselectivity. The configuration of the major adduct, *anti*-**12**, resulting from the diazomethane's approach to the less hindered face of the dipolarophile, was determined unequivocally by  $^1\text{H}$ -NMR (n.O.e.). Thus, in a way quite similar to that described above for cycloadducts derived from diazoethane, the n.O.e. value of 2.7 between the *ortho*-hydrogen atoms of the aromatic ring and the hydrogen atom on C- $\alpha$  to the sulfur function, gives evidence of the *syn*-arrangement of both substituents (proton and *p*-tolyl group) in compound **12** (Figure 3). Therefore, in adduct **13**, where the corresponding n.O.e. value was not detected, both groups must exhibit an *anti*-arrangement. If we consider that the configuration at sulfur must not be altered during the reaction, this analysis allowed us to determine the absolute configuration at all the chiral centers existing at the reaction products.



**Figure 3**

As we have seen, 1,3-dipolar cycloaddition reactions of (*R*)-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-ones **1** and **2** with diazoalkanes proceed in a completely regioselective way, usually with a high or complete  $\pi$ -facial selectivity and a good *exo*-selectivity (for diazoethane). In order to account for the observed  $\pi$ -facial diastereoselectivity, we assume that the favored approach of the dipole is to the less hindered face of the molecule, which is the one bearing the sulfur lone electron pair (Scheme 3), to afford the *anti*-adducts.



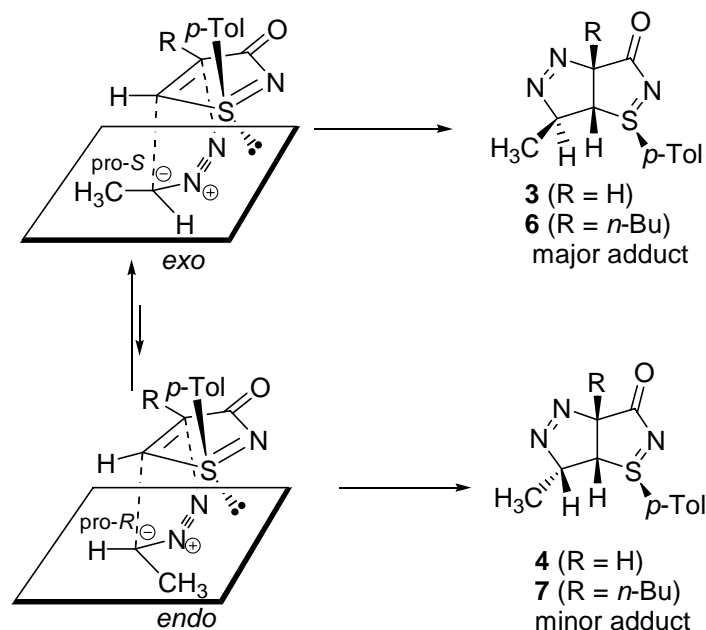
### Scheme 3

This behavior had also been observed in the Diels-Alder reactions of **1** and **2**.<sup>5,6</sup> However, in the latter case, the  $\pi$ -facial selectivity was always complete, whereas in reactions with diazoalkanes it depended on the experimental conditions and the dipoles used. The lower steric restrictions of the diazoalkanes with linear structures, with respect to that of the dienes can account for these differences.

As this selectivity has been explained on steric grounds, the relevance of these factors must be smaller in 1,3-dipolar reactions. This can easily be understood for diazoalkanes, owing to the linear structure of these dipoles. Otherwise, the evident larger size of diazoethane than that of diazomethane, would account for the smaller selectivity in Et<sub>2</sub>O/MeOH (entry 1, Table 3). This would also explain the complete facial selectivity observed in the reaction of **2** with diazoethane, which decreases for compound **1** (compare Tables 1 and 2, respectively).

In cycloadditions with diazoethane, an additional fact must be considered: the dipole approach to both faces of the sulfilimine may take place in two different ways, affording the *endo*- and *exo*- adducts. These two possible approaches to the face opposite to that bearing the *p*-tolyl group (*anti*- adducts) are depicted in Scheme 4. In the *exo*- approach, the methyl group of the dipole faces the hydrogen atom of the sulfilimine, whereas the hydrogen atom of the dipole faces the C—S bond of the dipolarophile. In the *endo* approach, the methyl group faces the C—S bond and the hydrogen atom of the dipole faces the hydrogen atom of the dipolarophile. The steric interactions existing in the *endo*- approach (Me/S and H/H) are more restrictive than those in the *exo*- one (Me/H and H/S). This explains why the approach of the sulfilimines to the pro-*S* face of diazoethane will be the favored one, yielding the *exo*- adducts as the major ones (Scheme 4). The fact that the *exo*- selectivity of these reactions is lower than that observed in the Diels-Alder reactions, where it is complete,<sup>5,6</sup> can also be explained on the basis of the lower steric restrictions existing with diazoalkanes.





Scheme 4

From all the results presented herein we can conclude that cyclic vinyl sulfilimines are interesting dipolarophiles in their reactions with diazoalkanes, producing  $\Delta^1$ -pyrazolines in a highly stereoselective manner. Concerning the  $\pi$ -facial selectivity, their behavior as dipolarophiles is complementary to that observed for (*Z*)-3-sulfinylacrylonitriles, but both the reactivity and stereoselectivity are higher than that reported for the corresponding nitriles. The search for conditions improving the reactivity and stereoselectivity of our sulfilimines, as well as the transformation of their adducts into cyclopropanes, are in progress and will be reported in due course.

## Experimental Section

**General Procedures.** All moisture-sensitive reactions were performed in flame-dried glassware equipped with rubber septa under positive pressure of argon. Silica gel 60 (230–400 mesh ASTM) and DC-Alufolien 60 F<sub>254</sub> were used for flash column chromatography and analytical TLC, respectively. Melting points were determined on a Gallenkamp apparatus in open capillary tubes and are uncorrected. Microanalyses were performed with a Perkin Elmer 2400 CHN and Perkin Elmer 2400 C-10II CHNS/O analyzers. NMR spectra were determined in CDCl<sub>3</sub> solutions, unless otherwise indicated, at 300- and 75 MHz for <sup>1</sup>H- and <sup>13</sup>C- NMR respectively; chemical shifts ( $\delta$ ) are reported in ppm and *J* values in Hertz. IR spectra frequencies are given in cm<sup>-1</sup>. Compounds **1** and **2** were synthesized and purified according to procedures described in ref. 5.

### 1,3-Dipolar cycloaddition reactions of vinyl *p*-tolylsulfilimines with diazoalkanes. General procedure

To a solution of vinyl *p*-tolylsulfilimine **1** or **2** (1 mmol, 1 equiv.) in 1 mL of dichloromethane, cooled at the temperature indicated in Tables 1–3, was added 3 mL of a 0.6 M solution of diazoalkane in diethyl ether. The resulting mixture was stirred under the conditions given in the Tables. The reaction was monitored by tlc and the solvent removed under reduced pressure.

**(3aR,6R,6aR)-6-Methyl-1-[(R)-*p*-tolyl]-6,6a-dihydro-1 $\lambda^4$ -pyrazolo[3,4-*d*]isothiazol-3(3aH)-one (*anti*-3-*exo*).** Obtained as the major product from the reaction of (*R*)-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**1**) with diazoethane. Yield 76% (from integration of well-separated signals of the <sup>1</sup>H-NMR spectrum of the crude reaction mixture). It could not be isolated diastereomerically pure. The characterization was performed on a mixture of *anti*-3-*exo*-, *anti*-4-*endo*- and *syn*-5-*exo*- isomers. IR (KBr): 2957, 2885, 2245, 1645, 1493, 1456, 1380, 1118, 1072, 889 cm<sup>-1</sup>. <sup>1</sup>H-NMR: 7.57 and 7.41 (AA'BB' system, 4H), 6.14 (dd, *J* 2.4 and 7.3, 1H), 5.34 (ddq, *J* 1.9 and 7.3, 1H), 2.80 (dd, *J* 1.9 and 7.3, 1H), 2.45 (s, 3H), 1.43 (d, *J* 7.5, 3H). <sup>13</sup>C-NMR: 187.9, 144.5, 131.4, 131.3, 125.7, 106.4, 91.4, 43.9, 21.5, 19.5. Anal. Calcd. for C<sub>12</sub>H<sub>13</sub>N<sub>3</sub>OS: C, 58.28; H, 5.30; N, 16.99; S, 12.97. Found: C, 58.47; H, 5.12; N, 16.71; S, 12.73%.

**(3aR,6S,6aR)-6-Methyl-1-[(R)-*p*-tolyl]-6,6a-dihydro-1 $\lambda^4$ -pyrazolo[3,4-*d*]isothiazol-3(3aH)-one (*anti*-4-*endo*).** Obtained from reaction of (*R*)-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**1**) with diazoethane. Yield 20% (determined by integration of well-separated signals in the <sup>1</sup>H-NMR spectrum of the crude reaction mixture): it could not be isolated diastereomerically pure. The characterization was performed on a mixture of *anti*-3-*exo*-, *anti*-4-*endo*- and *syn*-5-*exo*- isomers. <sup>1</sup>H-NMR: 7.57 and 7.41 (AA'BB' system, 4H), 6.25 (dd, *J* 1.9 and 8.0, 1H), 4.85 (ddq, *J* 1.9, 7.5 and 9.0, 1H), 3.19 (t, *J* 8.0, 1H), 2.45 (s, 3H), 1.78 (d, *J* 7.5, 3H). <sup>13</sup>C-NMR: 187.9, 144.5, 131.9, 131.3, 125.7, 109.2, 88.7, 39.9, 21.5, 14.5.

**(3aS,6S,6aS)-6-Methyl-1-[(R)-*p*-tolyl]-6,6a-dihydro-1 $\lambda^4$ -pyrazolo[3,4-*d*]isothiazol-3(3aH)-one (*syn*-5-*exo*).** Obtained as the minor product of the reaction of (*R*)-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**1**) with diazoethane. Yield 4% (determined by integration of well-separated signals of the <sup>1</sup>H-NMR spectrum of the crude reaction mixture). It could not be isolated diastereomerically pure. Its characterization was performed from a mixture of *anti*-3-*exo*-, *anti*-4-*endo*- and *syn*-5-*exo*-. <sup>1</sup>H-NMR: 7.57 and 7.41 (AA'BB' system, 4H), 6.10 (dd, *J* 1.9 and 8.9, 1H), 5.26 (ddq, *J* 1.9, 4.0 and 7.5, 1H), 3.45 (dd, *J* 4.0 and 8.1, 1H), 2.45 (s, 3H), 1.62 (d, *J* 7.5, 3H). <sup>13</sup>C-NMR: 187.9, 144.5, 131.4, 131.3, 125.7, 102.2, 90.3, 35.1, 21.5, 15.6.

**(3aR,6R,6aR)-3a-*n*-Butyl-6-methyl-1-[(R)-*p*-tolyl]-6,6a-dihydro-1 $\lambda^4$ -pyrazolo[3,4-*d*]isothiazol-3(3aH)-one (*anti*-6-*exo*).** Obtained diastereomerically pure by reaction of (*R*)-4-*n*-butyl-1-*p*-tolyl-1 $\lambda^4$ -isothiazol-3-one (**2**) with diazoethane followed by precipitation with diethyl ether. Yield 67%. White solid, mp 135–136 °C (ethyl acetate). [ $\alpha$ ]<sub>D</sub><sup>20</sup> +204.2 (*c* 0.5, CHCl<sub>3</sub>). IR (KBr) 2954, 2864, 2249, 1645, 1490, 1448, 1376, 1304, 1237, 1118, 1072, 889 cm<sup>-1</sup>. <sup>1</sup>H-NMR: 7.48 and 7.37 (AA'BB' system, 4H), 5.32 (dq, *J* 3.6 and 7.5, 1H), 3.17 (d, *J* 3.6, 1H), 2.52–2.37 (m, 1H), 2.42 (s, 3H), 2.02–1.90 (m, 1H), 1.61 (d, *J* 7.5, 3H), 1.28–1.18 (m, 2H), 0.87–0.68 (m, 2H), 0.74 (t, *J* 7.3, 3H). <sup>13</sup>C-NMR: 181.8, 144.0, 133.6, 131.0, 125.2, 107.3, 91.2, 68.1, 34.5,

27.4, 22.4, 21.4, 18.6, 13.6. Anal. Calcd. for C<sub>16</sub>H<sub>21</sub>N<sub>3</sub>OS: C, 63.33; H, 6.98; N, 13.85; S, 10.57. Found: C, 63.64; H, 7.10; N, 13.71; S, 10.78%. HRMS (FAB) calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>OS: 304.149235. Found: 304.149702. MS (FAB) 304 (26) [M + H]<sup>+</sup>, 276 (63), 177(42), 123 (36).

**(3aR,6S,6aR)-3a-n-Butyl-6-methyl-1-[(R)-p-tolyl]-6,6a-dihydro-1λ<sup>4</sup>-pyrazolo[3,4-d]-isothiazol-3(3aH)-one (anti-7-endo)**. Obtained as the minor cycloadduct from reaction of (R)-4-n-butyl-1-p-tolyl-1λ<sup>4</sup>-isothiazol-3-one (**2**) with diazoethane. When the *anti-7-exo* isomer was precipitated by treatment of the crude reaction mixture with diethyl ether, the remaining mixture in the mother liquors contained 12% of *anti-7-endo*- isomer (determined from the <sup>1</sup>H- NMR spectrum of the crude reaction mixture). It could not be isolated diastereomerically pure. Its characterization was performed on a mixture of *anti-6-exo*- and *anti-7-endo*- isomers. IR (KBr) 3020, 2961, 2924, 2240, 1495, 1452, 1307, 1090, 1043, 811, 795 cm<sup>-1</sup>. <sup>1</sup>H- NMR: 7.43 and 7.32 (AA'BB' system, 4H), 5.00 (dt, *J* 7.5 and 15.8, 1H), 3.65 (d, *J* 8.3, 1H), 2.52-2.37 (m, 1H), 2.44 (s, 3H), 2.02-1.90 (m, 1H), 1.94 (d, *J* 7.5, 3H), 1.28-1.18 (m, 2H), 0.87-0.68 (m, 2H), 0.69 (t, 3H). <sup>13</sup>C- NMR: 183.0, 143.9, 133.6, 130.9, 125.2, 107.0, 87.7, 67.4, 33.8, 26.7, 22.3, 21.3, 16.3, 13.5. HRMS (FAB) calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>2</sub>OS: 304.149235. Found: 304.149845. EM (FAB) 304 (26) [M + H]<sup>+</sup>, 276 (63), 177(42), 123 (36).

**(3aR,6aR)-1-(p-Tolyl)-6,6a-dihydro-1λ<sup>4</sup>-pyrazolo[3,4-d]isothiazol-3(3aH)-one (anti-12)**. Obtained as the major product of the reaction of (R)-1-p-tolyl-1λ<sup>4</sup>-isothiazol-3-one (**1**) with diazomethane. Yield 90% (determined by integration of well-separated signals of the <sup>1</sup>H- NMR spectrum of the crude reaction mixture). It could not be isolated diastereomerically pure. Its characterization was performed on a mixture of *anti-12* and *syn-13*. IR (KBr) 2959, 2890, 2242, 1645, 1493, 1468, 1380, 1072, 889 cm<sup>-1</sup>. <sup>1</sup>H- NMR: 7.59 and 7.40 (AA'BB' system, 4H), 6.13 (dt, *J* 2.2 and 7.5, 1H), 5.27 (dc, *J* 2.0 and 14.8, 1H), 4.69 (ddq, *J* 2.0, 8.7 and 18.8, 1H), 3.18 (ddd, *J* 2.0, 7.7 and 9.1, 1H), 2.43 (s, 3H). <sup>13</sup>C- NMR: 188.2, 144.3, 131.1 (3C), 125.7 (2C), 106.6, 82.6, 36.4, 21.2. Anal. Calcd. for C<sub>11</sub>H<sub>11</sub>N<sub>3</sub>OS: C, 56.63; H, 4.75; N, 18.01; S, 13.75. Found: C, 56.28; H, 4.61; N, 18.42; S, 13.27%.

**(3aS,6aS)-1-(p-Tolyl)-6,6a-dihydro-1λ<sup>4</sup>-pyrazolo[3,4-d]isothiazol-3(3aH)-one (syn-13)**. Obtained as the minor product of the reaction of (R)-1-p-tolyl-1λ<sup>4</sup>-isothiazol-3-one (**1**) with diazomethane. Yield 10% (by integration of the <sup>1</sup>H- NMR spectrum of the crude reaction mixture). It could not be isolated diastereomerically pure. Its characterization was performed on a mixture of *anti-12* and *syn-13*. <sup>1</sup>H- NMR: 7.49 and 7.38 (AA'BB' system, 4H), 6.07 (dq, *J* 8.3 and 1.4, 1H), 5.20-5.16 (m, 2H), 3.95 (ddd, *J* 6.1, 7.7 and 14.4, 1H), 2.42 (s, 3H). <sup>13</sup>C- NMR: 179.8, 142.9, 131.2, 125.7, 95.9, 82.6, 36.4, 21.4.

### Reactions of cycloadducts with LiAlH<sub>4</sub>. General procedure

A suspension of cycloadduct (1 mmol, 1 equiv.) and LiAlH<sub>4</sub> (1 mmol, 1 equiv.) in 2 mL of tetrahydrofuran was stirred under argon for 5 min. The reaction mixture was quenched with 2 mL of water-ethyl acetate-dichloromethane (1:1:2) and extracted with ethyl acetate (3×4 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed under reduced pressure.

**(3R,4R,5R)-3-*n*-Butyl-5-methyl-4-(*p*-tolylsulfenyl)-4,5-dihydro-3H-pyrazol-3-carboxamide (8).** Obtained by reaction of *anti*-6-*exo* with LiAlH<sub>4</sub>; purified by flash column chromatography using 3:1 hexane–ethyl acetate as the eluent. Yield 45%. White solid, mp 105–106 °C (ethyl acetate).  $[\alpha]_D^{20} +20.4$  (*c* 0.4, CHCl<sub>3</sub>). IR (KBr) 3024, 2964, 2035, 1665, 1490, 1448, 1376, 1304, 1237, 1118, 1072, 960 cm<sup>-1</sup>. <sup>1</sup>H-NMR: 7.36 and 7.13 (AA'BB' system, 4H), 6.06 (bs, 1H), 5.75 (bs, 1H), 4.66 (ddd, *J* 5.2, 7.5 and 14.7, 1H), 2.93 (d, *J* 5.2, 1H), 2.41–2.29 (m, 1H), 2.34 (s, 3H), 1.69–1.45 (m, 4H), 1.39–1.19 (m, 1H), 1.30 (d, *J* 7.5, 3H), 0.89 (t, *J* 7.3, 3H). <sup>13</sup>C-NMR: 169.8, 138.2, 133.6, 130.4, 129.9, 100.3, 91.9, 53.1, 39.8, 26.6, 22.9, 21.1, 18.7, 13.7. Anal. Calcd. for C<sub>16</sub>H<sub>23</sub>N<sub>3</sub>OS: C, 62.92; H, 7.59; N, 13.76; S, 10.5. Found: C, 63.22; H, 7.68; N, 13.71; S, 10.78%.

**(3R,4R,5R)-3-*n*-Butyl-5-methyl-4-(*p*-tolylsulfonyl)-4,5-dihydro-3H-pyrazol-3-carboxamide (9).** To a solution of 305 mg (1 mmol, 1 equiv.) of (3R,4R,5R)-3-*n*-butyl-5-methyl-4-(*p*-tolylsulfenyl)-4,5-dihydro-3H-pyrazol-3-carboxamide (8) in dichloromethane (10 mL), cooled at 0 °C, was added slowly 690.3 mg (2 mmol, 2 equiv.) of MCPBA (50% in water). The resulting mixture was stirred at 0 °C for 1 hour and then quenched with saturated sodium bisulfite (10 mL). The organic layer was washed with saturated sodium bicarbonate (10 mL) and the aqueous phase extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×15 mL). The organic extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated under reduced pressure. The residue was purified by flash column chromatography using a 2:1 mixture of hexane–ethyl acetate as the eluent. Yield 92%. White solid, mp 111–112 °C (diethyl ether).  $[\alpha]_D^{20} +58.3$  (*c* 1.0, CHCl<sub>3</sub>). IR (KBr): 3471, 3349, 3066, 2933, 2250, 1693, 1597, 1454, 1305, 1148, 911, 732 cm<sup>-1</sup>. <sup>1</sup>H-NMR: 7.75 and 7.36 (AA'BB' system, 4H), 6.06 (bs, 1H), 5.8 (bs, 1H), 5.25 (q, *J* 7.0, 1H), 3.08 (d, *J* 6.4, 1H), 2.46 (s, 3H), 2.25 (dt, *J* 3.2 and 10.7, 1H), 1.57–1.38 (m, 1H), 1.48 (d, *J* 7.0, 3H), 1.35–1.17 (m, 4H), 0.85 (t, *J* 7.0, 3H). <sup>13</sup>C-NMR: 167.9, 145.2, 136.4, 129.6, 128.3, 98.6, 85.9, 70.9, 40.7, 26.0, 22.7, 21.7, 18.9, 13.7. HRMS (FAB) calcd. for C<sub>16</sub>H<sub>24</sub>N<sub>3</sub>O<sub>2</sub>S: 338.1524. Found: 338.1518. MS (FAB): 338 (23) [M<sup>+</sup>+H], 293 (52), 219 (7), 154 (100), 109 (22), 81 (33).

**(3S,4S,5S)-3-*n*-Butyl-5-methyl-4-(*p*-tolylsulfonyl)-4,5-dihydro-3H-pyrazol-3-carbonitrile (10).** To a solution of 190 mg (0.5 mmol, 1 equiv.) of (3R,4R,5R)-3-*n*-butyl-5-methyl-4-(*p*-tolylsulfonyl)-4,5-dihydro-3H-pyrazol-3-carboxamide (9) in 4 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub>, cooled at 0 °C under argon, was added 202 mg (2 mmol, 4 equiv.) of triethylamine, then 211.6 mg (126.2 μL, 0.75 mmol, 1.5 equiv.) of triflic anhydride. The mixture was stirred for 1 h. at room temperature, hydrolyzed with water (4 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3×4 mL). The extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent evaporated under reduced pressure. Yield 57%. White solid, mp 102–104 °C (hexane–diethyl ether).  $[\alpha]_D^{20} = +93.9$  (*c* 0.5, CHCl<sub>3</sub>). IR (KBr): 2984, 2963, 2878, 2241, 1592, 1571, 1489, 1468, 1380, 1335, 1120, 1081 cm<sup>-1</sup>. <sup>1</sup>H-NMR: 7.85 and 7.42 (AA'BB' system, 4H), 5.20 (q, *J* 7.4, 1H), 2.92 (d, *J* 7.7, 1H), 2.47 (s, 3H), 1.83 (dt, *J* 11.5 and 5.5, 1H), 1.71 (dt, *J* 14.0 and 4.5, 1H), 1.48 (d, *J* 7.3, 3H), 1.60–1.20 (m, 4H), 0.85 (t, *J* 7.1, 3H). <sup>13</sup>C-NMR: 146.4, 134.6, 130.3, 128.9, 113.3, 89.0, 87.8, 70.4, 39.0, 26.1, 22.0, 21.7, 18.8, 13.5. HRMS (FAB) calcd. for C<sub>16</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>S: 320.1428. Found: 320.1432. MS (FAB): 342 (4) [M<sup>+</sup>+Na], 306 (6) [M<sup>+</sup>+1], 292 (13), 156 (34), 139 (100), 91 (30).

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9. The attempts to transform these compounds into more stable molecules, which might be isolated readily, were unsuccessful. In this sense, treatment of the adduct mixture, either with aluminum amalgam (in order to reduce the N=N double bond) or with LiAlH<sub>4</sub> (with the aim of transforming the *N*-acylsulfilimine into sulfenylcarboxamide) did not give the expected results, affording decomposition products in all cases.
10. The *endo/exo*- naming refers to the *cis*- and *trans*- arrangement, respectively, of the methyl group and the H-1 and H-2 atoms in the adducts.