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1,3-Dipolar Cycloadditions of Diazoalkanes to Activated Sulfoxides: Influence of Lewis Acids

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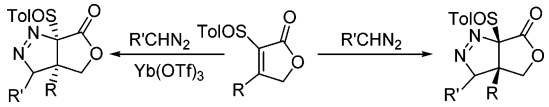
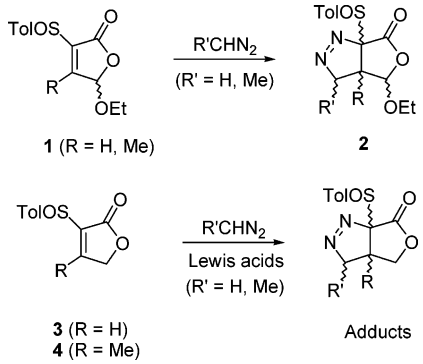


The reactions of diazomethane and diazoethane with (*S*)-3-*p*-tolylsulfinylfuran-2(5*H*)-one (**3**) and its 4-methyl derivative (**4**) have been studied. The sulfinyl group was able to completely control the π-facial selectivity of all these reactions, which decreased when the polarity of the solvent increased and could be inverted in the presence of Lewis acids, $Yb(OTf)_3$ being the most efficient catalyst. This behavior made possible the stereodivergent synthesis of diastereoisomeric pyrazolines in almost quantitative yields and de's higher than 98%. The *endo*/*exo* selectivity was also complete in reactions of **3** with diazoethane, whereas **4** afforded an easily separable 1:1 mixture of diastereoisomers. Steric factors accounts for the *endo*/*exo* selectivity, whereas electrostatic interactions must also be considered to explain the facial selectivity.

Introduction

The 1,3-dipolar cicloadditions of electron deficient olefins with diazoalkanes is one of the best known methods for preparing pyrazolines.[1] The asymmetric version of this reaction usually involves the use of electron-deficient olefins bearing different chiral auxiliaries,[2] which evolve with good or excellent stereoselectivities. However, the use of vinyl sulfoxides in asymmetric 1,3-dipolar reactions has been scarcely explored.[3] Several years ago we initiated a program to explore the applicability of vinyl sulfoxides in asymmetric 1,3-dipolar reactions. In this context we have investigated the reactions with nitrile oxides,[4] azomethine ylides,[5] nitrones,[6] and diazoalkanes.[7−9] In the last field we have reported excellent results from the two epimers at C-5 of 5-ethoxy-3-*p*-tolylsulfinylfuran-2(5*H*)-ones[7] (**1** in Scheme 1), which evolved into adducts **2** in a highly stereoselec

SCHEME 1



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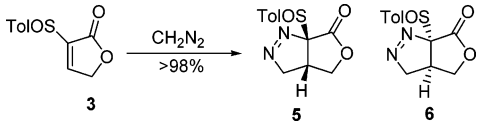
tive way and very good yields. Similar results were obtained in reactions of diazoalkanes with 3-sulfinylacrylonitriles[8] and 5-menthyloxy-4-phenylsulfinylfuran-2(5*H*)-one.[9] From all these results we concluded that the sulfinyl group exerted a strong influence of the course of these reactions, substantially improving the features of the furan-2(5*H*)-ones and acrylonitriles as chiral dipolarophiles. Otherwise, the use of Lewis acids as the catalysts of cycloaddition processes is widely spread,[2a,b,10] because they improve both the reactivity and the stereoselectivity.[10a,b] In some cases they are able to invert the facial selectivity, thus providing stereodivergent routes for two diastereoisomers from the same substrate. To evaluate the role of the Lewis acids on the course of the reactions of vinyl sulfoxides with diazoalkanes, we initially chose compounds **1** as the dipolarophiles. However, the addition of the Lewis acids caused the epimerisation at C-5 of furanones **1**, yielding complex mixtures. Consequently, we decided to use furanones **3** and **4** (Scheme 1), with no epimerizable C-5 as the dipolarophiles.

Additionally, the obtained results from **3** and **4** would clarify the actual role of the sulfinyl group on the course of these reactions because those observed from **1** were explained as a result of the mutual influence of the two chiral centers (sulfur and C-5). In this paper we describe the behavior of compounds **3** and **4** in their reactions with diazomethane and diazoethane under different conditions. The influence of different Lewis acid as the catalysts is also considered. This study has furnished one of the most efficient methods for the stereodivergent synthesis of enantiopure bicyclic pyrazolines derived from butenolides.

Results and Discussion

The synthesis of the starting sulfinylfuranones **3** and **4** had been previously reported.[11] Initially, we studied the reactions of compound **3** with diazomethane under different conditions (Table 1). All of these reactions (except for the reactions in THF at −40 or −78 °C, entries 4 and 8) evolved into mixtures of two compounds, **5** and **6**, which could be separated and identified as the two isomers resulting from the approach of the dipole to a different face of the dipolarophile. The yield was almost quantitative in all cases. The influence of different factors on the facial selectivity was investigated. It decreased when the polarity of the solvent increased (entries 1−4), the best results having been obtained in THF. By lowering the temperature it was possible to improve the stereoselectivity (entries 4−8), which was complete (de > 98%) at −40 °C in THF, affording compound **5** as the only product in 98% isolated yield (entry 4). The reactions

TABLE 1. Reactions of Compound 3 with Diazomethane under Different Conditions



3 **5** **6**

Entry	Solvent	T	Lewis Acid (equiv)	t	**5:6** ratio[a] (isolated yield)
1	MeOH	−40°C		30 min	75 (71): 25 (21)
2	MeCN	−40°C		30 min	78 (76): 22 (19)
3	$PhCH_3$	−40°C		45 min	87 (85): 13 (10)
4	**THF**	**−40 °C**		**30 min**	**100 (98): 0**
5	THF	−20°C		20 min	94 (92): 6 (3)
6	THF	0°C		10 min	88 (85): 12 (9)
7	THF	rt		5 min	85 (81): 15 (11)
8	**THF**	**−78 °C**		**2.5 h**	**100 (97): 0**
9	THF	−78°C	$ZnBr_2$ (1.2)	1 h	79 (76): 21 (17)
10	THF	−78°C	$BF_3.OEt_2$ (1.2)	55 min	92 (86): 8
11	THF	−78°C	$Eu(fod)_3$ (1.2)	35 min	Complex Mixture
12	THF	−78°C	$Eu(OTf)_3$ (1.2)	45 min	30:70 (67)
13	THF	−78°C	$Yb(OTf)_3$ (1.2)	50 min	20 (16): 80 (75)
14	THF	−40°C	$ZnBr_2$ (1.2)	40 min	92 (88): 8 (4)
15	THF	−40°C	$Yb(OTf)_3$ (1.2)	35 min	18 (14): 82 (79)
16	THF	−20°C	$ZnBr_2$ (1.2)	15 min	85 (81): 15 (12)
17	THF	−20°C	$Yb(OTf)_3$ (1.2)	10 min	21 (18): 79 (75)
18	THF	−78°C	$Yb(OTf)_3$ (0.5)	50 min	30:70
19	**THF**	**−78 °C**	**$Yb(OTf)_3$ (1.0)**	**30 min**	**13:87 (83)**
20	THF	−78°C	$Yb(OTf)_3$ (1.5)	20 min	20:80

[a] Determined by ^1H NMR.

were also performed in the presence of different Lewis acids at −78 °C (entries 9−13). The use of $ZnBr_2$ or $BF_3{\cdot}OEt_2$ slightly increased the rate of the cycloaddition but decreased the stereoselectivity (compare entries 9 and 10 with 8), whereas the use of $Eu(fod)_3$ afforded complex mixtures (entry 11). More interesting were the results obtained under $Eu(OTf)_3$ or $Yb(OTf)_3$ catalysis. The use of these catalysts also decreased the reaction times, but which is more important, it also inverted the sense of the stereoselectivity, determining the predominance of the isomer **6** in the reaction mixtures (entries 12 and 13). The influence of the catalysts was also evident at higher temperatures (entries 14−17). Once the best catalyst was determined, $Yb(OTf)_3$, we checked the influence of the amount of catalyst (entries 18−20), the best results having been obtained with ca. 1 equiv of the Lewis acid (entry 19), whereas with smaller (entry 18) or larger (entry 20) amounts of catalyst the observed de's became lower. As the yield of all of these reactions was almost quantitative and the separation of diastereoisomers was readily achieved, compound **6** could be isolated in 83% yield despite the fact that the reaction evolved with 74% de (entry 19).

Next we studied reactions of **3** with diazoethane (Table 2). In these reactions, only two, **7**-*exo* and **8**-*exo*, out of the four possible diastereoisomers were formed in practically quantitative yield and could be readily separated by chromatography. The comparison between Tables 1 (diazomethane) and 2 (diazoethane) reveals that both reactivity and facial selectivity were lower for diazomethane than for diazoethane. Hence, diazoethane reacted instantaneously with **3** even at −78 °C (entry 4, Table 2), whereas diazomethane required 2.5 h under similar conditions (entry 8, Table 1). The facial selectivity of the reactions with diazoethane at rt (entry 1, Table 2)

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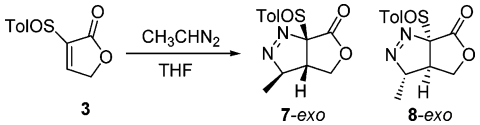
TABLE 2. Reactions of Compound 3 with Diazoethane under Different Conditions



Entry	T	Lewis Acid (equiv)	t	**7-*exo*:8-*exo*** ratio[a] (isolated yield)
1	rt		5 min	92 (87): 8 (4)
2	−20°C		5 min	94 (89): 6 (3)
3	−40°C		5 min	95(91): 5 (3)
4	**−78 °C**		**5 min**	**100 (95): 0**
6	−78°C	$Yb(OTf)_3$ (0.5)	5 min	21:79
7	**−78 °C**	**$Yb(OTf)_3$ (1.0)**	**5 min**	**<2: >98 (94)**
8	−78°C	$Yb(OTf)_3$ (1.5)	5 min	10:90

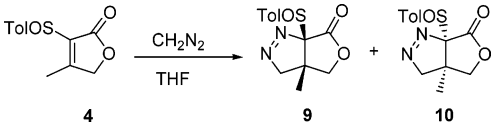
[a] Determined by ^1H NMR.

was larger than that observed with diazomethane (entry 7, Table 1). As expected, the facial selectivity of the reactions with diazoethane also increased when the temperature became lower (entries 1−4, Table 2), which allowed the formation of **7**-*exo* as the only adduct at −78 °C (95% isolated yield, entry 4). The most remarkable feature of the reactions with diazoethane was the exclusive formation of adducts designated as *exo*,[12] which means that the *endo*/*exo* selectivity was completely controlled. When the reactions were conducted under $Yb(OTf)_3$ catalysis, the facial selectivity was inverted (entries 5−8) but the *exo* adducts were also exclusively formed. As in the previous case, the best results were obtained by using 1 equiv of Lewis acid at −78 °C (entry 7). Under these conditions, compound **8**-*exo* could be obtained in 94% isolated yield in its optically pure form.

We also studied the reactions of the 4-methyl-substituted furanone **4** with diazoalkanes. Although the synthesis of **4** had been previously reported,[11b] we prepared it in a more convenient way by extrusion of nitrogen from any mixture of compounds **5** + **6** resulting from reactions in Table 1. These denitrogenation reactions occurred in quantitative yields when pyrazolines **5** and/or **6** were refluxed in toluene. The results obtained in reactions of **4** with diazomethane are collected in Table 3. Compound **4** was less reactive than **3** (compare data of reactions conducted under similar conditions in Tables 1 and 3). By contrast, the facial selectivity was much higher for **4**, which evolved with 94% de at rt (entry 1, Table 3), whereas a 70% de was attained for **3** under similar conditions (entry 7, Table 1). The complete control of the facial selectivity was achieved at −10 °C for **4** (entry 3, Table 3), but it required that the temperature be lowered to −40 °C for **3** (entry 4 Table 1). This behavior allowed the synthesis of enantiomerically pure **9** in 97% yield under the conditions of entry 3 (Table 3). As observed in reactions from **3** (Tables 1 and 2), the facial selectivity of compound **4** could be inverted in the presence of $Eu(OTf)_3$ or $Yb(OTf)_3$ (entries 4 and 5, Table 3). The best results were obtained at −40 °C under $Yb(OTf)_3$ catalysis (entry 8, 86% de), yielding **10** in 89% isolated yield.

(12) The *endo* or *exo* terms, indicative of the *cis* or *trans* arrangement of the methyl group of the diazoethane with respect to the furanone moiety at the pyrazoline ring, are related to the *endo* and *exo* addition modes of the dipole to the dipolarophile using as the reference the carbonyl group at the later.

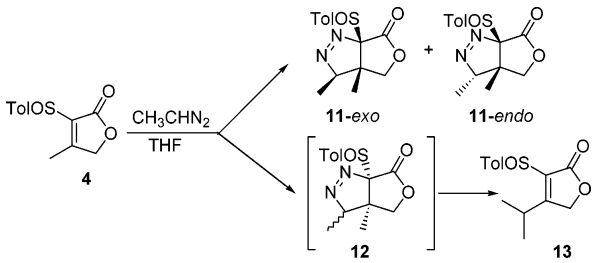
TABLE 3. Reactions of Compound 4 with Diazomethane under Different Conditions



Entry	T	Lewis Acid (equiv)	t (min)	**9**:**10** ratio[a] (isolated yield)
1	rt		45	97 (91): 3
2	0 °C		55	98 (94): 2
3	**−10 °C**		**65**	**100 (97): 0**
4	0 °C	$Eu(OTf)_3$ (1.2)	55	28:72 (66)
5	0 °C	$Yb(OTf)_3$ (1.2)	50	25:75 (69)
6	−10 °C	$Yb(OTf)_3$ (1.2)	60	12:88 (80)
7	−20 °C	$Yb(OTf)_3$ (1.2)	80	10:90 (83)
8	**−40 °C**	**$Yb(OTf)_3$ (1.0)**	**75**	**7:93 (89)**

[a] Determined by ^1H NMR.

TABLE 4. Reactions of Compound 4 with Diazoethane



Entry	Catalyst (equiv)	T	t (min)	**11**-*exo*: **11**-*endo*: **13** ratio[a] (isolated yields)
1		rt	55	50 (45): 50 (47):0
2		0 °C	72	50 (44): 50 (48): 0
3		−10 °C	100	50 (46): 50 (47): 0
4	$Yb(OTf)_3$ (1.2)	0 °C	50	15:15:70 (65)
5	$Yb(OTf)_3$ (1.2)	−10 °C	60	13:13:74 (68)
6	$Yb(OTf)_3$ (1.0)	−20 °C	55	10:10:80 (73)

[a] Determined by ^1H NMR

Finally we have studied the reactions of **4** with diazoethane (Table 4). As was the case with diazomethane, the dipolarophile **4** exhibited a lower reactivity and a better facial selectivity than **3**. Thus, the de observed in reaction of **4** at rt was 94%, whereas it was only 84% for **3** (compare entries 1 in Tables 2 and 4). On the contrary, the *endo*/*exo* selectivity, which was complete for **3**, was almost inexistent for **4**, which evolved into equimolecular mixtures of **11**-*exo* and **11**-*endo* adducts under all of the assayed conditions (entries 1−3, Table 4). The addition of $Yb(OTf)_3$ inverted the facial selectivity and the isomers **11** were now the minor ones, but the expected major compounds, **12**-*exo* and **12**-*endo*, could not be detected. Instead of them, the olefin **13** was obtained as the major component of the mixtures (entries 4−6, Table 4). It suggests that **13** resulted from the fast evolution of **12**-*exo* and **12**-*endo* under the reaction conditions. Selectivity was higher when the temperature decreased. However, under −10 °C the reactions were not clean and the yields were lower. The reaction rates of diazomethane and diazoethane with **4** were not significantly increased in the presence the Lewis acid (see Tables 3 and 4).

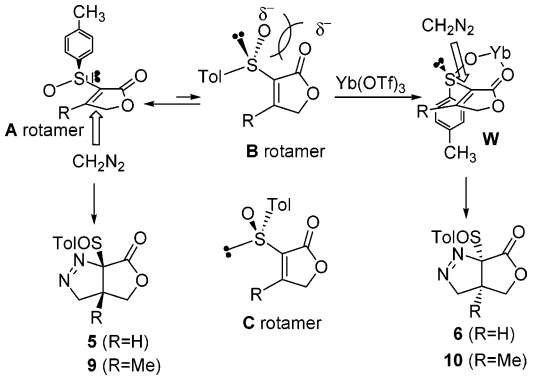
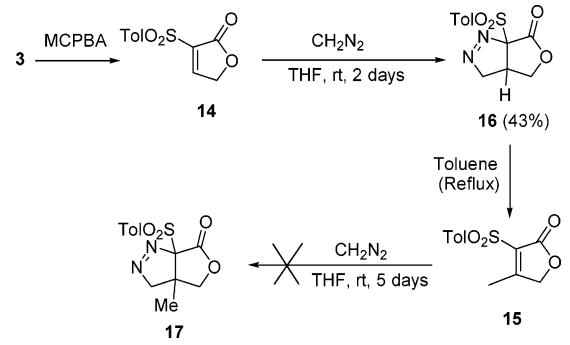


FIGURE 1. Rationalization of the facial selectivity observed in reactions with diazomethane.

Configurational Assignment. The structure of 6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo-[3,4-*c*]pyrazol-6-one was established for all of the adducts from their spectral data. The most relevant and general data for the assignment of the regiochemistry of the adducts were the δ values of the carbons common to pyrazoline and furanone rings. The existence of a quaternary carbon at 110−122 ppm, corresponding to C-6a, and the high $\Delta\delta$ (δC-3a−δC-6a) was only compatible with the regioisomer bearing the two electronegative atoms (sulfur and nitrogen) joined to the same carbon. The relative configuration at C-3 and C-3a of the adducts **7** and **8** could be unequivocally established from their $J_{3,3a}$ values (4 Hz), which showed a *trans* relationship between the involved protons. The configuration of C-3a and C-6a was assigned taking into account the effect of the *p*-tolylsulfinyl group on the π-facial selectivity for the addition of diazoalkanes to both epimers at C-5 of furanones **1**, which had been previously reported by us.[7] The higher chemical shift of C-6a in the [3a*S*,6a*R*,(S)*S*]-6*H*-furo[3,4-c]pyrazol-6-ones (**5**, **7**, **9**) than that in the corresponding 3a*R*,6a*S*,(S)*S* (**6**, **8**, **10**) stereoisomers agrees with the values observed for other 6*H*-furo[3,4-c]-pyrazol-6-ones. Additionally, the fact that in the presence of a Lewis acid the diazoalkane attacks the dipolarophile from the opposite face (vide infra) was also in agreement with the assigned stereochemistry for the adducts.

Stereochemical Proposals. The facial selectivity for reactions of diazomethane with compounds **3** and **4** can be rationalized from their conformational behavior and the different reactivity of the involved rotamers. The presumably most stable conformations of these dipolarophiles around the C−S bond are depicted in Figure 1. Electrostatic repulsion of the sulfinyl and carbonyl oxygens must destabilize **B** and **C** rotamers and favor the *s-cis* **A** conformations. The favored approach of the diazomethane to this rotamer will be that avoiding the steric interactions with the tolyl group, thus yielding adducts **5** or **9**. The negative influence of the solvent polarity on the facial selectivity of the reactions from **3** (it was lower in MeCN or MeOH than in THF or toluene, see Table 1) can be explained by assuming that the population of the rotamer **B** or **C** (Figure 1) must be higher in these solvents where the role of the electrostatic interactions is minimized. The population of the rotamer **C** must be low for compound **3** (R = H), because of the electrostatic and steric interactions of the substituents at sulfur with the carbonyl oxygen. When the reactions were conducted under $Yb(OTf)_3$ catalysis, the formation of the quelated species **W** changed the spatial arrangement of the tolyl group, thus inverting the facial selectivity of the reaction. Other catalysts must be less efficient to furnish **W** or prefer the formation of other species involving the association of the metal to only one of the oxygens at the dipolarophiles, where the spatial arrangement of the tolyl group is similar to that of **A** rotamers. The changes observed in the stereoselectivity for reactions conducted with different amounts of $Yb(OTf)_3$ can be explained by assuming that in the presence of 0.5 equiv of catalyst species **W** and **A** were present, and they evolved into different diastereoisomers. **W** must be the only species present when 1 equiv of the catalyst was used. The presence of an excess of the catalyst would favor the formation of species such as **A** but doubly associated, thus explaining the observed decrease in the stereoselectivity. A similar behavior of compound **3** had been observed in its Diels−Alder reactions catalyzed by Lewis acids.[11a] The same stereochemical model accounts for the facial selectivity observed in reactions of **3** and **4** with diazoethane.

SCHEME 2



The fact that the facial selectivity observed in reactions from **4** (R = Me in Figure 1) was even higher than that observed from **3** (R = H) is not easily rationalized. It could be explained by assuming that conformation **C** did not participate in these reactions, and the stereoselectivity would be only dependent on the relative population of **A** and **B**. The strong steric interaction $(Tol/Me)_{1,3-parallel}$ would account for the lower population of the **B** rotamer at compound **4** and, therefore, its higher facial selectivity. The scarce role of the conformers **C** in determining the stereoselectivity of the reactions of **3** (R = H) and **4** (R = Me) would be reasonable on steric and electrostatic grounds. Only the assumption that the reactivity of the **C** conformation was very low could explain its scarce influence on the stereoselectivity control. It is usually admitted that the strong steric hindrance of the bulky tolyl group inhibits the approach of the dipole to the face exhibiting such a group. By contrast, the size of the oxygen is not large enough to preclude the approach of the linear diazoalkane, unless the electrostatic repulsion of the sulfinyl oxygen toward the negatively charged nitrogen at the dipole also contribute to make it difficult.

To verify the assumption that the approach of diazoalkanes to any face occupied by the sulfinyl oxygen or the tolyl group would be strongly hindered, we have prepared the sulfones **14** and **15** (Scheme 2), any of whose possible conformations exhibits a tolyl group or a sulfonyl oxygen oriented toward the face of approach of the dipole.

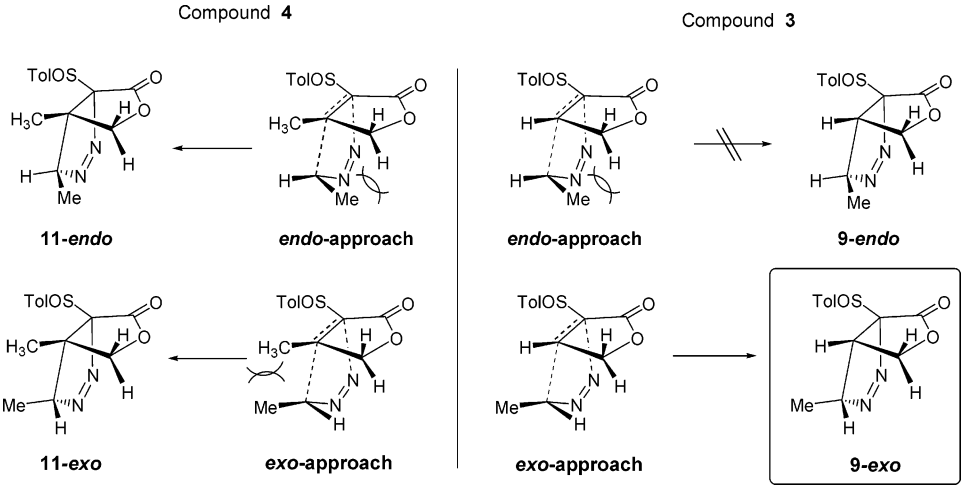


FIGURE 2. Rationalization of the *endo*/*exo* selectivity in reactions with diazoethane.

Their reactions with diazomethane were much slower than those of their corresponding sulfoxides. Compound **14** required 2 days to be transformed into **16** (43% yield and less than 50% of conversion), and **15** remained unaltered after 5 days at rt in the presence of diazomethane (**17** was not detected, Scheme 2). These results support the assumption on the scarce reactivity of conformations **C** of the sulfoxides **3** and **4** (Figure 1), since the electronic effect of the sulfonyl group should increase the dipolarophilic reactivity more that of the sulfinyl group.

Concerning the complete *exo* selectivity observed in reactions with diazoethane, steric interactions should account for the observed results. In Figure 2 are depicted the two possible approaches (*endo* and *exo*) of diazoethane to the favored face of compounds **3** and **4**. The most important interactions to be considered are those of the methyl group at the dipole with the substituents at C-4 of both furanones. These interactions are quite different in the case of compound **3** (Me/CH_2 for the *endo* approach and the much smaller Me/H for the *exo* one), thus determining its completely *exo*-selective evolution. By contrast, they are almost identical for compound **4** (Me/CH_2 for the *endo* approach and Me/Me for the *exo* one), thus explaining the complete absence of *endo*/*exo* selectivity observed in its reactions.

In summary, we have described the behavior of the sulfinyl furanones **3** and **4** with diazomethane and diazoethane under different conditions. The sulfinyl group was able to completely control the π-facial selectivity. The use of some Lewis acids as the catalysts, such as $Yb(OTf)_3$, substantially inverted the selectivity making possible the stereodivergent synthesis of pyrazolines. The *endo*/*exo* selectivity was controlled by steric effects and it was also complete in reactions starting from **3**. The excellent yields and the almost complete stereoselectivity indicated that these reactions were a satisfactory and efficient method for preparing enantiomerically pure pyrazolines derived from butenolides.

Experimental Section

1,3-Dipolar Cycloadditons. Method A. To a solution of 1 mmol of (S_S)-3-[(4-methylphenyl)sulfinyl]-2(5*H*)-one (**3**), or its corresponding 4-methyl derivative (**4**), in the solvent (2 mL) indicated in Table 1, cooled at the temperature indicated in Tables 1−4, was added an excess of an ethereal solution of diazomethane (0.95 M) (Tables 1 and 3) or diazoethane (0.95 M) (Table 2 or 4). The reaction was kept at the same temperature for the time indicated in Tables 1−4. The solvent was removed, and the residue was analyzed by ^{1}H NMR and purified as indicated in each case.

Method B. To a stirred solution of $Yb(OTf)_3$ (amounts indicated in Tables 1−4) in THF (0.1 M) at room temperature was added a solution of furanones **3** or **4** (0.5 mmol) in THF (5 mL). The mixture was stirred for 1 h and cooled at the corresponding temperature.Then was added an ethereal solution of diazomethane or diazoethane (0.95 M). The reaction was kept at the same temperature for the time indicated in Tables 1−4. The reaction was quenched with aqueous potassium sodium tartrate at the indicated temperature and extracted with AcOEt (3 × 8 mL). The organic extracts were washed with brine (7 mL) and dried ($MgSO_4$). The solvent was removed under vacuum. The resulting residue was analyzed by ^{1}H NMR and purified as indicated in each case.

(3a*S*,6a*R*,(S)*S*)-6a-[(4-Methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (5). Compound **5** was obtained from **3** and diazomethane (Table 1) and purified by flash chromatography (AcOEt−hexane, 1:1) and crystallized from AcOEt−hexane: mp 100−102 °C (white solid, 98% yield); $[\alpha]_D$ +65 (*c* 0.5, $CHCl_3$); IR (film) 1712, 1498, 1432; ^{1}H NMR (300 MHz) δ 7.64 and 7.39 (AA′BB′ system, 4H), 5.15 (dd, 1H, J = 19.0 and 9.4 Hz), 4.66 (dd, 1H, J = 19.0 and 4.0 Hz), 3.83 (dd, 1H, J = 9.9 and 3.5 Hz), 3.65 (dd, 1H, J = 9.9 and 8.3 Hz), 3.28−3.16 (m, 1H), 2.45 (s, 3H); ^{13}C NMR (75 MHz) δ 164.3, 143.6, 133.9, 130.5, 124.8, 120.9, 87.7, 72.3, 29.7, 21.4. Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.59; H, 4.62; N, 10.72; S, 12.31.

(3a*R*,6a*S*,(S)*S*)-6a-[(4-Methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (6). Compound **6** was obtained from **3** and diazomethane (Table 1), purified by flash chromatography (AcOEt−hexane, 1:1), and crystallized from AcOEt−hexane: mp 90−94 °C (white solid, 83% yield); $[\alpha]_D$ +228 (*c* 0.5, $CHCl_3$); IR (film) 1721, 1485, 1428; ^{1}H NMR (300 MHz) δ 7.41 and 7.30 (AA′BB′ system, 4H), 4.57 (m, 2H), 3.81 (m, 2H), 3.33 (m, 1H), 2.41 (s, 3H); ^{13}C NMR (75 MHz) δ 165.7, 143.8, 133.5, 129.7, 125.3, 118.6, 86.3, 72.6, 30.6, 21.4. Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.53; H, 4.58; N, 10.60; S, 12.13. Found: C, 54.71; H, 4.53; N, 10.82; S, 12.29.

(3*R*,3a*S*,6a*R*,(S)*S*)-3-Methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (7-*exo*). Compound **7-*exo*** was obtained from **3** and diazoethane (Table 2), purified by flash chromatography (AcOEt−hexane, 1:1), and crystallized from AcOEt−hexane: mp 97−98 °C (white solid, 95% yield); $[\alpha]_D$ +59 (*c* 0.5, $CHCl_3$); IR (film)

1758, 1471, 1456; ^{1}H NMR (200 MHz) δ 7.61 and 7.38 (AA′BB′ system, 4H), 4.77 (qd, 1H, J = 7.3 and 4.0 Hz), 3.92 (dd, 1H, J = 9.7 and 3.0 Hz), 3.54 (dd, 1H, J = 9.7 and 8.3 Hz), 2.67 (ddd, 1H, J = 8.3, 4.0, and 3.0 Hz), 2.43 (s, 3H), 1.62 (d, 3H, J = 7.3); ^{13}C NMR (50 MHz) δ 164.3, 143.7, 133.9, 130.4, 124.6, 121.3, 96.3, 71.8, 37.0, 21.4, 18.1. Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.10; H, 5.11; N, 9.99; S, 11.81.

(3*S*,3a*R*,6a*S*,(S)*S*)-3-Methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (8-*exo*). Compound **8-*exo*** was obtained from **3** and diazoethane (Table 2), purified by flash chromatography (AcOEt−hexane, 1:1), and crystallized from AcOEt−hexane: mp 89−91 °C (white solid, 82% yield); $[\alpha]_D$ +239 (*c* 0.5, $CHCl_3$); IR (film) 1763, 1467, 1453; ^{1}H NMR (200 MHz) δ 7.46 and 7.33 (AA′BB′ system, 4H), 4.62 (qd, 1H, J = 7.3 and 4.0 Hz), 4.56 (dd, 1H, J = 9.7 and 8.3 Hz), 4.09 (dd, 1H, J = 9.7 and 2.7 Hz, 1H), 2.63 (ddd, 1H, J = 8.3, 4.0, and 2.7 Hz), 2.41 (s, 3H), 0.77 (d, 3H, J = 7.3 Hz); ^{13}C NMR (50 MHz) δ 165.4, 143.3, 133.2, 129.2, 125.4, 119.5, 94.8, 71.6, 37.6, 21.4, 18.3. Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.22; H, 5.18; N, 10.26; S, 11.83.

(3a*S*,6a*R*,(S)*S*)-3a-Methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (9). Compound **9** was obtained from **4** and diazomethane (Table 3), purified by flash chromatography (AcOEt−hexane, 1:1), and crystallized from Et_2O: mp 125−127 °C (white solid, 97% yield); $[\alpha]_D$ +111 (*c* 0.5, $CHCl_3$); IR (film) 1769, 1541, 1457; ^{1}H NMR (200 MHz) δ 7.75 and 7.42 (AA′BB′ system, 4H), 5.13 (d, 1H, J = 18.3 Hz), 4.46 (d, 1H, J = 18.3 Hz), 4.19 (AB system, 2H), 2.47 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (50 MHz) δ 163.1, 143.4, 133.8, 129.5, 126.7, 108.7, 91.8, 74.1, 47.2, 21.6, 18.1. Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.48; H, 5.18; N, 10.25; S, 11.30.

(3a*R*,6a*S*,(S)*S*)-3a-Methyl-6a-[(4-methylphenyl)sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (10). Compound **10** was obtained from **4** and diazomethane (Table 3), purified by flash chromatography (AcOEt−hexane, 1:1), and crystallized from Et_2O−pentane: mp 109−111 °C (white solid, 89% yield); $[\alpha]_D$ +289 (*c* 0.5, $CHCl_3$); IR (film) 1775, 1520, 1446; ^{1}H NMR (200 MHz) δ 7.56 and 7.28 (AA′BB′ system, 4H), 5.34 (d, 1H, J = 11.6 Hz), 5.02 (d, 1H, J = 11.6 Hz), 4.62 (d, 1H, J = 9.9 Hz), 4.11 (d, 1H, J = 9.9 Hz), 2.45 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (50 MHz) δ 164.8, 143.6, 133.6, 129.2, 127.1, 108.3, 91.5, 74.2, 47.6, 21.4, 17.7; MS (FAB$^+$) *m/z* 279 (M + 1, 100), 251 (53), 131 (12); HRMS (FAB) calcd for $C_{13}H_{15}N_2O_3S$ 279.3279 [M + H], found 279.3284.

(3*R*,3a*S*,6a*R*,(S)*S*)-3,3a-Dimethyl-6a-[(4-methylphenyl)-sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (11-*exo*). Compound **11-*exo*** was obtained from **4** and diazoethane (Table 4), purified by flash chromatography (AcOEt−hexane, 1:3), and crystallized from Et_2O: mp 135−137 °C (yellow solid, 46% yield); $[\alpha]_D$ +89 (*c* 0.5, $CHCl_3$); IR (film) 1756, 1443, 1431; ^{1}H NMR (200 MHz) δ 7.75 and 7.41 (AA′BB′ system, 4H), 4.29 (q, 1H, J = 7.3), 4.13 (s, 2H), 2.46 (s, 3H), 1.72 (d, 3H, J = 7.3), 1.46 (s, 3H); ^{13}C NMR (50 MHz) δ 162.7, 142.9, 134.4, 129.1, 127.3, 109.5, 92.5, 74.0, 50.0, 21.5, 17.6, 16.6; MS (FAB$^+$) *m/z* 293 (M + 1, 100), 265 (31); HRMS (FAB) calcd for $C_{14}H_{17}N_2O_3S$ 293.0882 [M + H], found 293.0888.

(3S,3a*S*,6a*R*,S_S)-3,3a-Dimethyl-6a-[(4-methylphenyl)-sulfinyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (11-*endo*). Compound **11-*endo*** was obtained from **4** and diazoethane (Table 4), purified by flash chromatography (AcOEt−hexane, 1:3): colorless oil; 48% yield; $[\alpha]_D$ +256 (*c* 0.5, $CHCl_3$); IR (film) 1772, 1515, 1465; ^{1}H NMR (200 MHz) δ 7.76 and 7.41 (AA′BB′ system, 4H), 5.02 (q, 1H, J = 7.5 Hz), 4.17 (AB system, 2H), 2.46 (s, 3H), 1.47 (s, 3H), 1.33 (d, 3H, J = 7.5 Hz); ^{13}C NMR (50 MHz) δ 163.2, 142.8, 134.4, 129.1, 127.3, 110.0, 95.4, 72.6, 47.1, 21.5, 17.7, 16.5; MS (FAB$^+$) *m/z* 293 (M + 1, 100), 265 (48), 127 (9); HRMS (FAB) calcd for $C_{14}H_{17}N_2O_3S$ 293.0882 [M + H], found 293.0888.

[(S)*S*]-4-Isopropyl-3-[(4-methylphenyl)sulfinyl]furan-2(5*H*)-one (13). Compound **13** was obtained from **4** and diazoethane (entry 6, Table 4). The residue was crystallized from Et_2O−pentane: mp 115−116 °C (yellow solid, 73% yield); $[\alpha]_D$ +123 (*c* 0.5, $CHCl_3$); IR (film) 1748; ^{1}H NMR (200 MHz) δ 7.59 and 7.30 (AA′BB′ system, 4H), 4.67 (AB system, 2H), 3.12 (m, 2H), 2.42 (s, 3H), 1.30 (d, 3H, J = 7.1 Hz), 1.22 (d, 3H, J = 7.1 Hz); ^{13}C NMR (50 MHz) δ 173.1, 165.2, 142.0, 139.7, 130.1, 129.8, 125.3, 73.6, 26.2, 21.4, 18.9, 16.1. Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10; S, 12.13. Found: C, 63.59; H, 6.13; S, 12.01.

3-[(4-Methylphenyl)sulfonyl]furan-2(5*H*)-one (14). To a solution of (±)-3-*p*-tolylsulfinylfuran-2(5*H*)-one[13] in CH_2Cl_2 (0.1 M) was added a solution of *m*-CPBA (1.2 equiv) in CH_2Cl_2 (0.1 M) for 1 h at room temperature. The reaction was quenched with a $NaHSO_3$ solution (0.1 mmol/1 mL) and then washed with saturated aqueous sodium bicarbonate (0.1 mmol/1 mL). The organic extracts were dried ($MgSO_4$), and the solvent was removed under vacuum. It crystallized from Et_2O: mp 164−165 °C dec (white solid, 96% yield); IR (film) 1758; ^{1}H NMR (acetone-d_6, 300 MHz) δ 8.63 (t, 1H, J = 1.5 Hz), 7.97 and 7.52 (AA′BB′ system, 4H), 5.19 (s, 2H), 2.50 (s, 3H); ^{13}C NMR (75 MHz) δ 171.9, 162.1, 146.6, 132.1, 131.5, 130.7, 129.6, 71.3, 21.6. Anal. Calcd for $C_{11}H_{10}O_4S$: C, 55.45; H, 4.23; S, 13.46. Found: C, 55.33; H, 4.35; S, 12.39.

6a-[(4-Methylphenyl)sulfonyl]-3,3a,4,6a-tetrahydro-6*H*-furo[3,4-*c*]pyrazol-6-one (16). To a solution of **14** (1 mmol) in THF (2 mL) at room temperature was added an excess of an ethereal solution of diazomethane (0.95 M). The reaction was stirred at the same temperature for 2 days. The solvent was removed under vacuum. The residue was crystallized from AcOEt−hexane: mp 107−109 °C (white solid, 43% yield); IR (film) 1721, 1492, 1438; ^{1}H NMR (300 MHz) δ 7.90 and 7.45 (AA′BB′ system, 4H), 5.23 (dd, 1H, J = 19.0 and 8.9 Hz), 4.85 (dd, 1H, J = 19.0 and 3.6 Hz), 4.64 (dd, 1H, J = 9.7 and 8.5 Hz), 3.96 (dd, 1H, J = 9.7 and 3.8 Hz), 3.78 (m, 1H), 2.50 (s, 3H); ^{13}C NMR (50 MHz) δ 163.0, 147.1, 131.2, 131.0, 129.8, 115.5, 87.5, 70.9, 34.2, 21.9; MS (FAB$^+$) *m/z* 281 (M + 1, 100), 252 (65), 99 (5); HRMS calcd for $C_{12}H_{13}N_2O_4S$ [M + H] 281.0518, found 281.0517.

4-Methyl-3-[(4-methylphenyl)sulfonyl]furan-2(5*H*)-one (15). A solution of **16** (0.5 mmol) in toluene (15 mL) was refluxed for 3 h. The solvent was evaporated, and the residue was crystallized from Et_2O: mp 176−178 °C (white solid, 90% yield); IR (film) 1764, 1425, 1398; ^{1}H NMR (300 MHz) δ 7.97 and 7.35 (AA′BB′ system, 4H), 4.75 (s, 2H), 2.56 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (50 MHz) δ 171.8, 166.3, 145.6, 136.2, 129.8, 128.7, 128.5, 72.5, 21.7, 13.8. Anal. Calcd for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.79; S, 12.71. Found: C, 57.40; H, 4.69; S, 13.03.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds **10**, **11-*exo***, **11-*endo***, and **16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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