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Diels–Alder reactions of [(S)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene with monosubstituted ethylenes

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Abstract: Diels–Alder reactions of [(S)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene with 1-pyrrolidinyl-1-cyclohexene and methyl acrylate evidenced: i) low reactivity of the diene regardless of the electronic character of the dienophile (high pressures were always required); ii) a complete regio- and *endo*-selectivity (both controlled by the sulfoxide), but a low π-facial diastereoselectivity in the cycloaddition with enamine; iii) diastereoselectivity (facial and *endo/exo*) for the reaction with methyl acrylate is dependent on the regiochemistry (mainly controlled by the methyl substituent). © 1997 Elsevier Science Ltd

The increasing interest of asymmetric Diels–Alder reactions with sulfinyl dienophiles is due to the achievement of efficient control of the diastereoselectivity.[1] By contrast, reactions with enantiomerically pure sulfinyldienes have received much less attention[2] in spite of their synthetic potential. In preceding papers, we have studied the Diels–Alder reactions of 1-*p*-tolylsulfinyldienes with dienophiles such as N-methylmaleimide[3] and maleic anhydride[2a] showing a high π-facial diastereoselectivity for such cycloadditions. An additional interesting feature of these reactions was the spontaneous [2,3]-sigmatropic rearrangement of the allylic sulfoxide in the adducts which opens an easy access to highly functionalized cyclohexenols,[3,4] not easily available by other ways. Applications of these tandem reactions were limited by the low reactivity of these dienes with electron poor dienophiles which required high pressures and/or long reaction times. Taking into account the expected electron withdrawing character of the sulfinyl group, this low reactivity was not surprising. According to previous work of Evans[4] on racemic 1-phenylsulfinylbutadiene, inverse electron demand Diels–Alder reactions with dienophiles such as vinylethers and enamines should run better. The high stereoselectivity observed for the reactions with maleimide[3] or maleic anhydride,[2a] had been explained on the base of strong electrostatic repulsions between the oxygen atoms of diene and dienophile in the transition state leading to the resulting adducts. In order to support this explanation, the study of dienophiles unable to exhibit such interaction in the TS was necessary. In this paper we report the results obtained in reactions of enantiomerically pure [(S)*R*]-(1*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene **1** with ethyl vinyl ether, 1-pyrrolidinyl-1-cyclohexene and methyl acrylate which allowed us to clarify several of the mentioned questions as well as to establish the regiochemistry of the cycloadditions with 1-sulfinyl substituted dienes.

All attempts to achieve the cycloaddition between enantiomerically pure diene **1**[3,5] and ethyl vinylether (different solvents, temperatures, Lewis acids and high pressures) were unsuccessful.[6] Compound **1** reacted with 1-pyrrolidinyl-1-cyclohexene **2** in refluxing acetonitrile[7] giving a complex mixture where the cycloadducts could only be detected in trace amounts. A clean reaction was achieved when a mixture of diene **1** and enamine **2** (6 eq) was submitted to high pressure (13 Kbar) in ether solution. The results are shown in Scheme 1.

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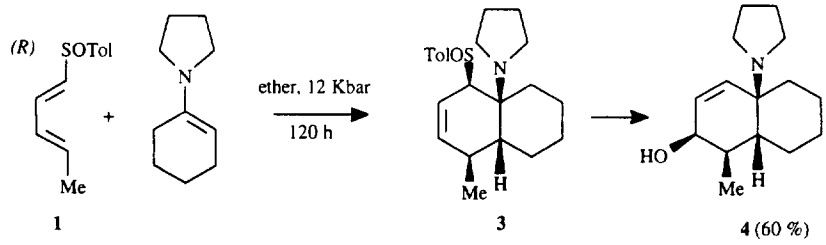
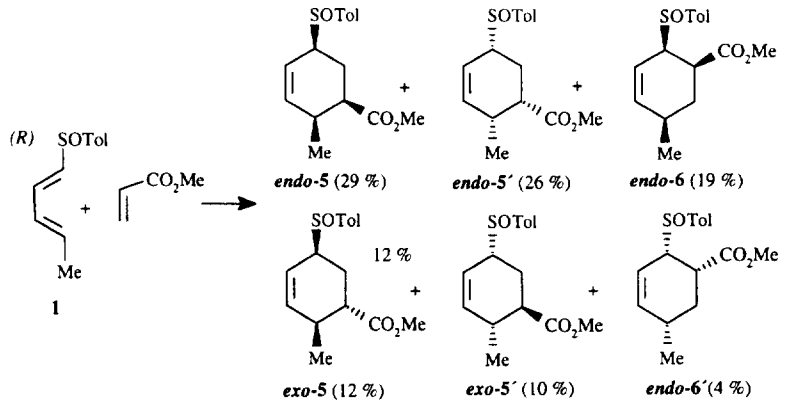


Scheme 1.

Long reactions times (5 days) were required to complete the cycloaddition. Cyclohexenol **4**,[8] resulting from the adduct **3** through a sulfoxide–sulfenate rearrangement,[9] was isolated in 60% yield. After shorter periods of time mixtures of **3**, the rearranged carbinol **4** and the starting diene **1** resulted. The isolation of **3** was not possible owing to its instability and ready conversion into **4** under the reaction conditions used (the excess of enamine **1** could act as thiophilic agent). The enantiomeric excess (28%) as well as the absolute configuration of **4** were determined via the MTPA esters.[10] The exclusive formation of **4** evidenced that the sulfinyl group controls both the regioselectivity and *endo*-selectivity, but its low enantiomeric excess revealed a rather low π-facial diastereoselectivity for the initial cycloaddition.

Diene **1** did not react with methyl acrylate either under thermal conditions (the dienophile itself and water[11] were used as solvents) or in the presence of different catalysts ($LiClO_4$[10] and $LiClO_4$ dispersed on silicagel[12]). Once again, the cycloaddition only took place under high pressure conditions (11 Kbar, 64 h) yielding a complex mixture of regioisomeric adducts **5** and **6** (Scheme 2) which were purified by flash chromatography (hexane/AcOEt: 4/1). Adducts ***endo*-5** and ***endo*-5′** were isolated as a mixture in 43% yield. ***Exo*-5** and ***endo*-6** were obtained as pure diastereoisomers in 7% and 17% yield respectively and ***exo*-5′** and ***endo*-6′** were also obtained as a mixture (10%) after additional PLC. The structures and relative configurations could be established by NMR[8] and chemical correlation (mainly oxidation into sulfones).



Scheme 2.

From the ratios of the different adducts obtained by ^{1}H-NMR of the crude mixture, (Scheme 2) the following points could be established:

(1) Regioisomeric adducts **5** are predominant (**5/6**=72/23) indicating that the methyl group of **1** has a higher ability to control the regioselectivity than the sulfinyl one.

(2) The moderate *endo* selectivity (***endo*-5+*endo*-5′/*exo*-5+*exo*-5′**=55/22) of cycloaddition giving *ortho* adducts **5** became almost complete for the cycloaddition leading to the opposite regioisomers **6**.[13] This fact revealed a high *endo* orientating character of the sulfinyl group.

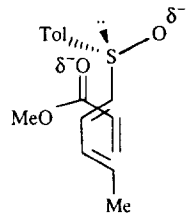


Figure 1.

(3) The π-facial diastereoselectivity observed in the formation of regioisomers **5** was low both for *endo* (***endo*-5/*endo*-5′**=29/26) and *exo* (***exo*-5/*exo*-5′**=12/10) approaches. On the other hand, a much higher π-facial selectivity (***endo*-6/*endo*-6′**=19/4) was observed for the *endo* approach yielding regioisomers **6**. The low π-facial selectivity resulting in the formation of compounds **5** was not unexpected according to the results obtained in the cycloadditions of acrolein or phenyl vinyl ketone with racemic 1-acylamino-4-sulfinyl substituted systems where the regiochemistry was fully controlled by the acylamino substituent (a 1:1 mixture of diastereoisomers was formed).[14] In both *endo* and *exo* approaches giving regioisomers **5**, the distance between the sulfinylic oxygen of **1** and the methoxycarbonyl substituent of methyl acrylate in the transition state, precluded any interaction controlling the π-facial selectivity. On the contrary, such interaction is feasible in the pathways affording regioisomers **6**. Now, the strong electrostatic repulsion between the oxygens of sulfoxide and ester groups determined the favored spatial arrangement shown in Figure 1 where such repulsion is minimized in the transition state. This disposition resulted in a most efficient control of the diastereoselectivity.[15] The low diastereofacial selectivity achieved in the reaction with the enamine could be due to the absence of such interactions in the transition state.

The low reactivity of the sulfinyldiene **1** with both electron rich and electron poor dienophiles, illustrates an unusual influence of the sulfinyl group on diene reactivity. The low reactivity of vinylsulfoxides as dienophiles was attributed to the simultaneous electron-donating (+M) and electron-withdrawing (−I) character of the sulfinyl group.[1c,16] In the case of dienes, this double effect could be responsible for a minimal influence on both LUMO and HOMO energies (+M and −I effects are mutually compensated[17]) which does not significantly facilitate the reactions with either electron deficient dienophiles (governed by the $HOMO_{diene}-LUMO_{dienophile}$ interaction) or electron rich dienophiles (governed by $LUMO_{diene}-HOMO_{dienophile}$ interaction).

Acknowledgements

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6. Ethyl vinylether did not react with 1-phenylsulfonyl, 4-*p*-tolylsulfinyl-1,3-butadiene,[4] an even more electron defficient diene than **1**, under very different thermal and catalytic [$SnCl_4$, $ZnBr_2$,Eu(fod)$_3$ and Yamamoto's catalyst (see Maruoka, K., Itoh, T., Sakurai, M., Nonoshita, K., Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 3588)] conditions. A 3:2 mixture of two adducts resulting from the *endo* approach of dienophile to both faces of diene could be obtained in very low yield (<20%) when the reactions were conducted under 12 Kbar.
7. These conditions had been successfully used by Evans[4] in the reaction of racemic 1-phenylsulfinylbutadiene with an enamine.
8. Characterization data: **4** $[\alpha]_D^{20}$=+7 (c=0.58, $CHCl_3$, 28% ee), ^{1}H-NMR ($CDCl_3$) δ 5.97 (dd, 1H, J=10 and 5 Hz), 5.78 (d, 1H, J=10 Hz), 3.90 (t, 1H, J=4.3 Hz), 2.8–1.2 (m, 18H), 1.02 (d, J=6.4 Hz). ***endo*-5+*endo*-5′**: ^{1}H-NMR ($CDCl_3$): δ 7.55 and 7.32, 7.50 and 7.30 (AA′BB′ syst, 4H, *p*-tol **5** and **5′**); 6.10–5.96 (m, 1H, H_3 o H_4, **5** and **5′**); 5.80–5.67 (m, 1H, H_3 o H_4, **5** and **5′**); 3.67 (s, 3H, MeO, **5** and **5′**); 3.51–3.43 (m, 1H, H_5, **5** and **5′**); 2.74–2.61 (m, 2H, H_1 y H_2, **5** and **5′**); 2.42 y 2.41 (s, 3H, CH_3-Ar, **5** and **5′**); 1.95–1.73 (m, 2H, H_6, **5** and **5′**); 0.82 (d, 3H, J=6.9, CH_3-, **5′**); 0.76 (d, 3H, J=6.9, CH_3-, **5**). ^{13}C-NMR ($CDCl_3$): δ 173.75 (*C*O_2Me), 142.8 and 142.7 (*C*-arom), 138.3 and 137.9 (C4), 129.5 and 129.7 (*C*H-arom), 124.9 and 125.1 (*C*H-arom), 119.9 and 119.4 (C3), 62.0 and 61.6 (C5), 51.6 (*C*H_3-O-), 42.2 and 42.1 (C1), 30.9 (C2), 21.3 (*C*H_3-arom), 18.9 and 16.8 (C6), 15.6 and 15.7 (*C*H_3-C1). ***Exo*-5**: m.p. 115–116°C (ether–hexane), $[\alpha]_D^{20}$=+479.4 (c 0.68, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 7.31 and 7.49 (AA′BB′ syst, 4H); 5.95 (ddd, 1H, J_{3-4}=10.0, J_{3-5}=1.9, J_{3-2}=2.5, H_3); 5.52 (dddd, 1H, J_{4-3}=10.0, J_{4-5}=4.5, J_{4-2}=2.9, J_{4-6e}=1.5, H_4); 3.67 (s, 3H, MeO); 3.41–3.37 (m, 1H, H_5); 2.52–2.41 (m, 1H, H_1); 2.41 (s, 3H, CH_3-Ar); 2.35 and 2.20 (m, 2H,H_2 y H_{6a}); 2.03 (ddd, J_{6a-6e}=14.7, J_{6a-1}=11.7, J_{6a-5}=6.2, H_{6a}); 0.99 (d, 3H, J=7, CH_3-). ^{13}C-NMR ($CDCl_3$): δ 164.3 (*C*O_2Me), 141.65 (*C*-arom), 139.7 (C4), 138.7 (*C*-arom), 129.6 and 124.8 (*C*H-arom), 117.8 (C3), 59.8 (C5), 51.7 (*C*H_3-O-), 43.3 (C1), 32.3 (C2), 25.4 (*C*H_3-arom), 21.4 (C6) and 19.8 (*C*H_3-C1). ***Exo*-5′** (from a mixture of ***endo*-6′** and ***exo*-5′**): ^{1}H-NMR: δ 7.55 and 7.32 (AA′BB′ syst, 4H, *p*-tol); 5.82 (dt, 1H, J_{3-4}=10.1, J_{3-5}=J_{3-2}=1.6, H_3); 5.02 (dda, 1H, $J_{4,3}$=10.1, $J_{4,5}$=3.5, H4); 3.72 (s, 3H, MeO); 3.38–3.26 (m, 1H, H_5); 2.68–2.54 (m, 3H, H_1, H_2, H_{6e}); 2.43 (s, 3H, CH_3-Ar); 2.08–2.01 (m, 1H, H_{6a}); 1.05 (d, 3H, J=7, CH_3-). ^{13}C-NMR ($CDCl_3$): δ 175.2 (*C*O_2Me), 142.04 and 140.07 (*C*-arom), 139.4 (C4), 129.7 and 125.3 (*C*H-arom), 118.7 (C3), 62.3 (C5), 51.8 (*C*H_3-O-), 43.3 and 32.8 (C2 and C1), 24.5 (*C*H_3-arom), 21.4 (C6) and 19.7 (*C*H_3-C1). ***Endo*-6**: m.p. 74–75°C (ether–hexane); $[\alpha]_D^{20}$=+692.7 (c 0.69, $CHCl_3$); IR (KBr): 3030, 2980, 1732, 1492, 1433, 1282, 1085 and 1046 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 7.47 and 7.30 (AA′BB′ syst, 4H, *p*-tol); 6.11 (da, 1H, J_{3-4}=9.9, H_4); 5.17 (ddd, 1H, J_{3-4}=9.9, J_{3-2}=5.3, J_{3-5}=2.4, H_3); 3.82 (s, 3H, MeO); 3.70–3.64 (m, 1H, H_2); 3.06 (ddd, 1H, J_{1-6a}=13.5, J_{1-2}=4.8, J_{1-6a}=3.1, H_1); 2.42 (s, 3H, CH_3-Ar); 2.40–2.25 (m, 1H, H_5); 2.25–2.12 (m, 1H, H_{6e}); 1.84 (ddd, 1H, J_{6a-6e}=14.5, J_{6a-1}=2.3, $J_{6a,5}$=10.8, H_{6a}); 1.12 (d, 3H, J=6.9, CH_3-). ^{13}C-NMR ($CDCl_3$): δ 173.0 (*C*O_2Me), 142.7 (C3), 140.7 and 140.3 (*C*-arom), 129.6 and 123.9 (*C*H-arom), 114.7 (C4), 63.9, 43.4 and 31.5 (C5, C2 and C1), 52.0 (*C*H_3-O-), 28.6 (*C*H_3-arom), 21.33 and 21.15 (*C*H_3-C1 and C6). ***Endo*-6′** (from a mixture of ***endo*-6′** and ***exo*-5′**): ^{1}H-NMR ($CDCl_3$): δ 7.55 and 7.28 (AA′BB′ syst, 4H, *p*-tol); 5.78–5.71 (m, 1H, H_4); 4.98–4.88 (m, 1H, H_3); 3.82 (m, 1H, H_2); 3.80 (s, 3H, MeO); 3.06–2.98 (m, 1H, H_1); 2.42 (s, 3H, CH_3-Ar); 2.30–2.15 (m, 1H, H_5); 1.78 and 1.59 (m, 2H, H_6); 1.01 (d, 3H, J=6.7, CH_3-). ^{13}C-NMR ($CDCl_3$): δ 172.85 (*C*O_2Me), 142.15 and 139.70 (*C*-arom), 138.7

(C3), 129.6 and 126.02 (*C*H-arom), 118.6 (C4), 65.3 (C2), 52.10 (*C*H_3-O-), 41.6 and 32.3 (C5 and C1), 24.5 (*C*H_3-arom), 21.4 (C6) and 20.9 (*C*H_3-C1).

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15. The fact that the π-facial selectivity with acrylate was high (***endo*-6/*endo*-6′**=19/4) but not complete, as it had been observed with maleimides[3] could be due to a negative influence of the high pressures (required in the first reaction) on the stereoselectivity and/or to the different structure of the substituent at dienophile (the free rotation of the ester group at dienophile, which could interact with the almost coplanar tolyl group at sulfoxide, is less feasible in maleimide owing to the restrictions imposed by the rigid maleimide system). In addition, the observance of the spectroscopic signals corresponding to ***endo*-6′** could be the result of the interconversion between ***endo*-6** and the sulfur epimer of ***endo*-6′** (through a sulfoxide–sulfenate–sulfoxide rearrangement). In this sense, some experiences suggest that the proportion of ***endo*-6′** increased with longer reaction times. Additional efforts are being made to clarify these points, but the conclusion about the higher π-facial selectivity of the reactions yielding regioisomers **6** appears as immutable.
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17. The complete regioselectivity observed in reactions with enamine suggests a slight predominance of the −I effect.

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