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Regiochemical Control in Asymmetric Diels-Alder Cycloadditions of Enantiopure (S)*S*-(*p*-Tolylsulfinyl)-1,4-benzoquinones with Dane's Diene

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Abstract: Enantiopure sulfinylquinones (+)-**2** and (+)-**3** reacted with Dane's diene **1** under thermal and $ZnBr_2$ Lewis acid conditions with reversal regiochemistry but similar π-facial diastereoselectivity to afford, after spontaneous elimination of the sulfinyl group, tetracyclic derivatives **4-9**.

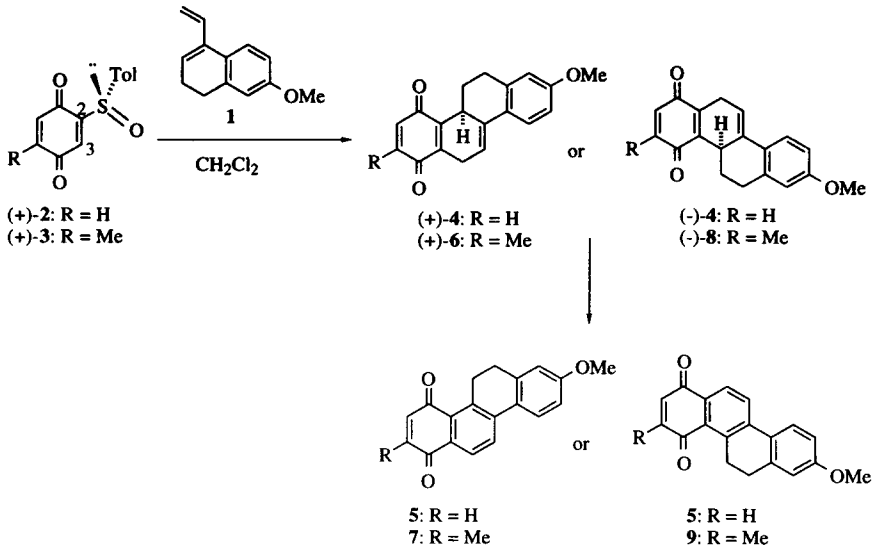
In the course of our work related to the asymmetric Diels-Alder reactions of (S)*S*-(*p*-tolylsulfinyl)-quinones, we had observed remarkable π-facial diastereoselectivities with a wide range of cyclic and acyclic dienes.[1] The regiochemical outcome of these reactions was studied with 1-substituted dienes,[1a,b] but the behaviour of differently substituted vinylcyclohexenes remained unknown. Such derivatives are of great interest since they open an easy access to highly substituted polycyclic quinones.[1f,2] Among them, the well known 6-methoxy-1-vinyl-3,4-dihydronaphthalene (Dane's diene) (**1**),[3] with activating substituents at C-1 and C-2, is one of the most frequently used in the construction of steroid systems.[4a,b] Moreover, the regioselectivity of its cycloadditions could be inverted by the use of Lewis acid catalysts.[4]

In order to know the regiochemistry of Dane's diene cycloadditions with sulfinylquinones, we undertook the study of its Diels-Alder reactions with enantiopure derivatives (+)-**2**[5] and (+)-**3**[6] (Table 1), under thermal conditions and in the presence of Lewis acids. In this letter we report the results of this study.

Thermal reaction between diene **1** and (S)*S*-2-(*p*-tolylsulfinyl)-1,4-benzoquinone (**2**) (Table 1, entry 1) took place on the C_2-C_3 substituted double bond of the quinone to gave compound (+)-**4**,[7,8] after spontaneous elimination of the sulfinyl group in the initially formed cycloadduct, with a quantitative conversion. Nevertheless, compound **4** was not stable enough and evolved during the isolation process into a mixture of **4** and aromatic derivative **5**. Both compounds could be separated after flash chromatography.

The same reaction in the presence of $ZnBr_2$ (Table 1, entry 2) afforded the corresponding enantiomer (-)-**4**[7,8] and aromatic compound **5**, after flash chromatography. Since no substituent remained in the quinonic moiety, the formation of (-)-**4** could be a consequence of a change in the regiochemistry or in the π-facial diastereoselectivity of the process. According to literature data related to the use of Dane's diene,[4] the former reason seemed more suitable, but our earlier observation of a reversed π-facial selectivity of the Diels-Alder reactions with cyclopentadiene and cyclohexadiene in the presence of $ZnBr_2$ could point to the latter.[1a,e]

Table 1. Diels-Alder Reactions of Dane's Diene **1** and Sulfinylquinones (+)-**2** and (+)-**3**



Entry	Dienophile	Lewis acid (equiv)	T (°C)	t (h)	Products (% Isolated yield)
1	(+)-**2**	-------	-78	24	(+)-**4** (23) + **5** (23)
2	(+)-**2**	$ZnBr_2$ (2)	-20	0.25	(-)-**4** (20) + **5** (25)
3	(+)-**3**	-------	-20	4	(+)-**6** (43) + **7** (24)
4	(+)-**3**	$ZnBr_2$ (2)	-20	2	(-)-**8** (38) + **9** (22)
5	(+)-**3**	$BF_3{\cdot}OEt_2$ (5)	-20	0.25	(+)-**6** + (-)-**8**[a]

[a]Obtained as a 25:75 mixture of **6** and **8**.

In order to ascertain the cause of the change in the rotary power of compound **4**, we carried out the cyloaddition between diene **1** and (S)*S*-2-methyl-5-(*p*-tolylsulfinyl)-1,4-benzoquinone (+)-(**3**). Under thermal conditions (Table 1, entry 3), a sole regioisomer (+)-**6**,[7-9] resulting from the spontaneous elimination of the sulfinyl group in the initially formed cycloadduct, was obtained. After flash chromatography, compound (+)-**6** and aromatic derivative **7** were isolated. This regiochemical outcome (*ortho*-adduct preferred) showed that, under thermal conditions, the alkyl substituent at C-1 of the diene directed the regiochemistry of the process.

When the cycloaddition of diene **1** and sulfinylquinone (+)-**3** was carried out in the presence of $ZnBr_2$ (Table 1, entry 4) we obtained tetracyclic quinone (-)-**8**,[7-9] whose structure showed the opposite regiochemistry than (+)-**6**. After flash chromatography, compound (-)-**8** and aromatic derivative **9** were isolated. This result (*meta*-adduct preferred) indicated that the *p*-methoxyphenyl substituent at C-2 of Dane's diene was controlling the regiochemistry of the Diels-Alder reactions under Lewis acid conditions. This observation was confirmed when the reaction of **1** and (+)-**3** was carried out in the presence of $BF_3{\cdot}OEt_2$ (Table 1, entry 5). In this case, a 25:75 mixture of regioisomers (+)-**6** and (-)-**8** was obtained, being (-)-**8** predominant.[10]

The change of regiochemistry observed in the presence of Lewis acids for substituted quinone (+)-**3** must be also expected for reactions of unsubstituted quinone (+)-**2**. Moreover, the fact that compounds (-)-**4** and (-)-**8**, only differing in the presence of a methyl group at C-2, exhibit negative rotary powers, suggested that the absolute configuration of both derivatives was the same. On these assumptions, we could conclude that π-facial diastereoselectivities of these cycloadditions were identical in the absence or in the presence of Lewis acids.[11] According to our previous results obtained in cycloadditions of sulfinylquinones with simple vinylcyclohexene derivatives,[1f] the absolute configuration of the new stereogenic centers should be *(S)* in compounds (+)-**4** and (+)-**6**, and *(R)* in (-)-**4** and (-)-**8**, as a result of the *endo* approach of the diene to the sulfinyl dienophile from the upper face containing the less sterically demanding lone electron pair at sulfur in the *s-cis* conformation of (+)-**2** and (+)-**3** represented in the Table. This conformation should be the most reactive both in the *ortho* and *meta* approaches, the latter occurring in the presence of Lewis acids.

The Frontier Orbital approach[12] has been previously invoked to explain the inversion of regiochemistry observed in reactions of **1** with 2,6-dimethyl-*p*-benzoquinone.[4b] The changes occurring from thermal to Lewis acid conditions were attributted to the reversed polarization of the LUMO of the dienophile due to a different basicity and accesibility of the quinonic carbonyl groups for the catalyst. This explanation is not valid for the parent 2,5-dimethyl-*p*-benzoquinone, which exhibited similar changes of regioselectivity despite the carbonyl groups are identically accesible for the Lewis acid.[4b] Considering these observations as well as the results obtained with sulfinylquinones, the origin of the reversed regiochemistry seems to be associated to the diene partner. The coordination of the catalyst to the methoxy group of **1** could induce significant changes in the coefficients of its HOMO, justifying the regiochemical control exerted by the activating substituent at C-2.

In conclusion, the Diels-Alder cycloadditions of Dane´s diene with sulfinylquinones proceeded with opposite regioselectivities but the same π-facial diastereoselection under thermal conditions and in the presence of $ZnBr_2$. The tandem Diels-Alder cycloaddition/spontaneous sulfoxide elimination provided an easy and regiocontrolled entry to optically active tetracyclic quinones **4**, **6** and **8**, as well as to aromatic derivatives **5**, **7** and **9**. Starting from unsubstituted sulfinylquinone (+)-**2**, both enantiomers of **4** are available by changing the reaction conditions. We are currently investigating the origin of the different enantiomeric excesses observed in these cycloadditions.

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7. All new compounds were characterized on the basis of their IR, ^{1}H-NMR (300 MHz, $CDCl_3$) and ^{13}C-NMR (75 MHz, $CDCl_3$) spectral data. (+)-**4**: mp 158-159 °C; $[\alpha]^{20}_D$ = +94 (*c* 0.12, $CHCl_3$), e.e. = 80%; ^{1}H-NMR δ 7.38 (d, 1H, *J* = 8.5 Hz), 6.76 (dd, 1H, *J* = 2.9 and 8.5 Hz), 6.75 (s, 2H), 6.65 (d, 1H, *J* = 2.9 Hz), 5.93 (m, 1H), 3.80 (s, 1H), 3.53-3.40 (m, 1H), 3.32-2.83 (m, 4H), 2.51-2.40 (m, 1H), 1.70-1.50 (m, 1H). (-)-**4**: $[\alpha]^{20}_D$ = -42 (*c* 0.12, $CHCl_3$), e.e. = 36%. **5**: mp 187-188 °C; ^{1}H-NMR δ 8.09 and 8.00 (AB system, 2H, *J* = 8.2 Hz), 7.69 (d, 1H, *J* = 8.6 Hz), 6.91 (s, 2H), 6.85 (dd, 1H, *J* = 2.8 and 8.6 Hz), 6.83 (d, 1H, *J* = 2.8 Hz), 3.87 (s, 3H), 3.53 and 2.83 (2dd, 4H, *J* = 7.0 and 7.4 Hz). (+)-**6**: mp 128-129 °C; $[\alpha]^{20}_D$ = +134 (*c* 0.13, $CHCl_3$), e.e. = 80%; ^{1}H-NMR δ 7.38 (d, 1H, *J* = 8.5 Hz), 6.74 (dd, 1H, *J* = 2.4 and 8.5 Hz), 6.64 (d, 1H, *J* = 2.4 Hz), 6.59 (q, 1H, *J* = 1.6 Hz), 5.95 (m, 1H), 3.80 (s, 1H), 3.52-3.35 (m, 1H), 3.32-2.82 (m, 4H), 2.53-2.41 (m, 1H), 2.06 (d, 3H, *J* = 1.6 Hz), 1.68-1.51 (m, 1H). **7**: mp 138-139 °C; ^{1}H-NMR δ 8.08 and 7.95 (AB system, 2H, *J* = 8.2 Hz), 7.67 (d, 1H, *J* = 8.6 Hz), 6.88 (dd, 1H, *J* = 2.6 and 8.6 Hz), 6.81 (d, 1H, *J* = 2.6 Hz), 6.76 (q, 1H, *J* = 1.4 Hz), 3.86 (s, 3H), 3.52 and 2.81 (2dd, 4H, *J* = 6.9 and 7.4 Hz), 2.14 (d, 3H, *J* = 1.4 Hz). (-)-**8**: mp 114-115°C; $[\alpha]^{20}_D$ = -185 (*c* 0.21, $CHCl_3$), e.e. > 95%; ^{1}H-NMR δ 7.37 (d, 1H, *J* = 8.5 Hz), 6.75 (dd, 1H, *J* = 2.4 and 8.5 Hz), 6.65 (d, 1H, *J* = 2.4 Hz), 6.59 (q, 1H, *J* = 1.6 Hz), 5.95 (m, 1H), 3.80 (s, 1H), 3.54-3.37 (m, 1H), 3.31-2.81 (m, 4H), 2.51-2.35 (m, 1H), 2.07 (d, 3H, *J* = 1.6 Hz), 1.69-1.50 (m, 1H). **9**: mp 181-182 °C; ^{1}H-NMR δ 8.05 and 7.95 (AB system, 2H, *J* = 8.2 Hz), 7.67 (d, 1H, *J* = 8.6 Hz), 6.89 (dd, 1H, *J* = 2.7 and 8.6 Hz), 6.80 (d, 1H, *J* = 2.7 Hz), 6.78 (q, 1H, *J* = 1.6 Hz), 3.87 (s, 3H), 3.50 and 2.81 (2dd, 4H, *J* = 7.0 and 7.5 Hz), 2.19 (d, 3H, *J* = 1.6 Hz).
8. The enantiomeric excesses of (+)-**4**, (-)-**4**, (+)-**6** and (-)-**8** were evaluated by ^{1}H-NMR analysis using Yb(hfc)$_3$ as chiral lantanide shift reagent. Racemic compounds necessary for such evaluation were obtained starting from racemic quinones (±)-**2** and (±)-**3**.
9. The structures of (+)-**6** and (-)-**8** were assigned from HMBC and HMQC spectral data and the regiochemistry of aromatic compound **7**, which resulted from (+)-**6**, was confirmed by X-ray difraction.
10. When this reaction was carried out with minor amounts of $BF_3{\cdot}OEt_2$ and/or lower temperatures, the ratio between (+)-**6** and (-)-**8** changed in favour of **6**, showing a decreasing association between the Lewis acid and the basic centre of diene **1**.
11. In the case of compound **4**, a change in both regiochemistry and π-facial diastereoselectivity from thermal to Lewis acid conditions would give the same enantiomer.
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