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HIGHLY DIASTEREOSELECTIVE DIELS-ALDER REACTION OF OPTICALLY ACTIVE 2-*p*-TOLYLSULPHINYL-2-CYCLOALKENONES WITH CYCLOPENTADIENE

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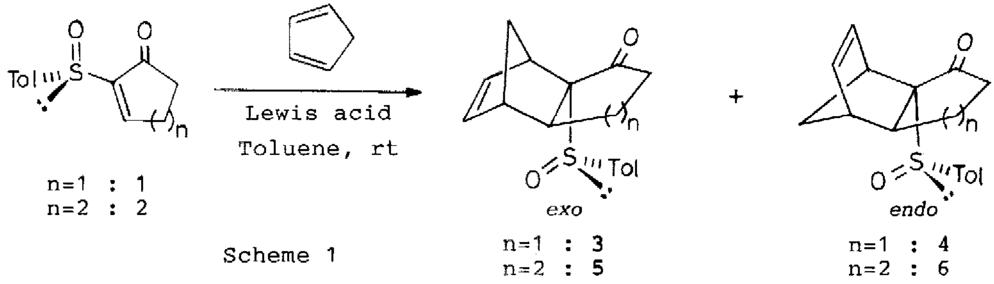
SUMMARY: The Diels-Alder reaction of (S)-2-*p*-tolylsulphinyl-2-cyclopentenone (and 2-cyclohexenone) with cyclopentadiene, catalized by $AlCl_3$ and $AlEtCl_2$, occurs at room temperature with complete facial diastereoselectivity, but with moderate *endo-exo* selectivity.

Substituted enantiomerically pure α,β- unsaturated sulphoxides have currently received considerable attention as chiral dienophiles[1] and chiral Michael acceptors as well.[2] Especially, the cycloalkenone sulphoxides **1** and **2**, reported by Posner,[3] have been widely used in asymmetric Michael additions and nicely applied to the enantioselective synthesis of several natural products.[4] Nevertheless, there is no example, to the best of our knowledge, in which 1 or **2** are used in asymmetric Diels-Alder reactions. We hereby report the highly diastereoselective catalyzed cycloaddition of cyclopentadiene to cycloalkenones 1 and **2**.

Our first attempts were carried out under thermal conditions, but no reaction took place at room temperature and decomposition of the dienophile was observed in refluxing toluene. We therefore, used Lewis acid catalysts (Scheme 1). The reactions were performed in toluene at r.t. using a small equimolecular excess of Lewis acid[5] and a large excess of cyclopentadiene (5 equiv.). The most significant results are presented in Table 1.

So far, $AlCl_3$ and $EtAlCl_2$ proved to be the best Lewis acid used (73-92% yield of pure adducts). Remarkably, only two cycloadducts were formed in all cases[6] (Table 1). The obtained diastereoisomeric pairs (**3-4** and **5-6**) were easily separated by flash chromatography on silica gel and their *endo* or *exo* stereochemistry were established from their unambiguous ^1H and ^{13}C-nmr data.[7] In the case of **5** and **6**, their stereochemistry was unequivocally confirmed by chemical correlation (Scheme 2). Thus, reductive elimination of the sulphinyl group in **5** and **6** with aluminium amalgam[8] (r.t., 2 h.) gave **7** and **8** respectively, whose ^1H and ^{13}C-nmr data were identical to those previously reported for racemic **7** and **8**, obtained by direct cycloaddition of 2-cyclohexenone with cyclopentadiene.[9]



Scheme 1

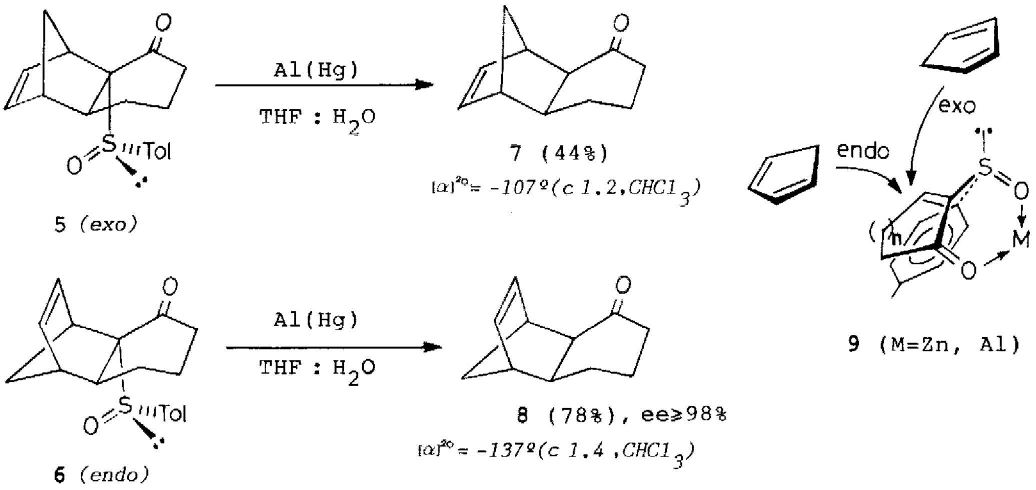
Table 1. Results obtained in reactions of **1** and **2** with cyclopentadiene.

Dienophile	Lewis Acid[a] (equiv)	Reaction time (h)	Yield[b] (%)	*exo/endo*[c]
1	$AlCl_3$ (1.1)	5	73	38/62
2	$AlCl_3$ (1.1)	10	75	68/32
1	$EtAlCl_2$ (1.2)	1	92	60/40
2	$EtAlCl_2$ (1.1)	2	77	83/17
2	$ZnBr_2$ (1.2)[d]	96	25	57/43

[a] With other Lewis acid, such as $BF_3.Et_2O$, Cl_4Ti or Et_2AlCl, many by-products were obtained. [b] After silica gel chromatography. [c] Determined by 200MHz ^1H-nmr on the crude mixture. [d] Carried out in CH_2Cl_2. 48% of unaltered **2** was recovered.

Therefore, these Diels-Alder reactions took place with virtually complete diastereofacial selectivity, showing the outstanding efficiency of *p*-tolylsulphinyl group as chiral auxiliary. Unfortunately, the *exo/endo* selectivity was only moderate (13-60% *d.e.*), the highest being observed when **2** was used as diene and $ElAlCl_2$ as catalyst (*exo* adduct is favoured, see Table 1). This *exo/endo* selectivity may be attributed to steric destabilization of *endo* approach between the CH_2 fragment on diene and the 2-substituent on cycloalkenone.[9] The size increase of the sulphinyl group when associated to $EtAlCl_2$ should be larger compared to $AlCl_3$, justifying the observed influence of Lewis acid on the *exo/endo* selectivity. On the other hand, the fact that dienophile **2** reacted more slowly than **1** could explain the stereoselectivity differences observed between them.

We have inferred the absolute configuration of the cycloadducts **3-6** shown in Scheme 1 from Posner's well established model,[3] which is able to explain the high diastereoselectivity observed in the Lewis acid catalized addition of nucleophiles to the cycloalkenones **1** and **2** in terms of a metal-chelated conformer **9** (Scheme 2). In this chelate, the β-ketosulphoxides are locked into a *syn* conformation , which hinder the approach of the nucleophile from one of the two faces. According to this, cyclopentadiene addition on **9** should take place only from the unhindered upper face, what would justify the exclusive formation of only one *exo* and only one *endo* cycloadducts. Similar chelated models have been proposed in the Diels-Alder reaction of chiral *p*-tolylsulphinylacrylates.[10]



Scheme 2

In order to check whether dienophiles were configurationally stable in the used reaction conditions, we have measured the optical purity of one of the ketones obtained in the reduction of the adducts. Acetalation of **8** with (R,R)-(-)-butane-2,3-diol under standard conditions[11] gave a single acetal whose ^{1}H-nmr spectrum showed a diastereomeric purity exceeding 98%[12] and, hence, demonstrated that sulphur did not epimerize before cycloaddition.

In conclusion, the complete facial diastereoselectivity observed in the catalyzed Diels-Alder reaction of **1** and **2** with cyclopentadiene indicates that these cycloalkenone sulphoxides are potentially useful chiral dienophiles. The application of these adducts in asymmetric synthesis and the study of the Diels-Alder reaction with other dienes are in progress in our laboratory.

ACKNOWLEDGEMENTS

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(5) The reactions were run out at 0.2-1.5 mmole scale under argon atmosphere. Cyclopentadiene was added after a 10 min. complexation time between the dienophile and the catalyst and the reactions were monitored by tlc. The use of other solvents (CH_2Cl_2, CH_3NO_2 or THF) or different amounts of Lewis acid (0.5, 1.0 or 2.0 eq.) gave less satisfactory results.

(6) The crude mixtures were studied by 200 MHz ^{1}H-nmr showing olefinic signals well separated (only one pattern for each *endo* or *exo* isomer can be seen).

(7) Compound **3**: $[\alpha]^{20} = +47^{0}$ (c 0.94, $CHCl_3$); ^{13}C-nmr ($CDCl_3$): 21.43 (CH_3), 22.97 (CH_2), 42.43 (CH_2), 44.19 (CH), 45.62 (CH_2), 48.82 (CH), 50.15 (CH), 82.14 (C), 124.92 (CH), 129.98 (CH), 135.54 (CH), 136.97 (C), 140.20 (CH), 142.21 (C) and 221.29 ppm (CO).
Compound **4**: $[\alpha]^{20} = +30^{0}$ (c 0.58, $CHCl_3$); ^{13}C-nmr ($CDCl_3$): 21.32 (CH_2), 21.48 (CH_3), 41.43 (CH_2), 44.77 (CH), 47.83 (CH), 48.43 (CH), 49.37 (CH_2), 81.35 (C), 125.40 (CH), 130.03 (CH), 137.15 (CH), 137.42 (CH), 142.37 (C) and 212.61 ppm (CO).
Compound **5**: $[\alpha]^{20} = +233^{0}$ (c 0.99, $CHCl_3$); ^{13}C-nmr ($CDCl_3$): 19.12 (CH_2), 21.38 (CH_3), 28.70 (CH_2), 38.85 (CH), 40.27 (CH_2), 45.75 (CH_2), 49.32 (CH), 50.48 (CH), 78.54 (C), 125.73 (CH), 129.60(CH), 134.30 (CH), 136.92 (C), 139.29 (CH), 142.70 (C) and 203.95 ppm (CO).
Compound **6**: $[\alpha]^{20} = +90^{0}$ (c 0.56, $CHCl_3$); ^{13}C-nmr ($CDCl_3$): 19.76 (CH_2), 21.42 (CH_3), 27.11 (CH_2), 40.33 (CH_2), 41.60 (CH), 44.91 (CH_2), 48.27 (CH), 48.93 (CH), 78.65 (C), 125.73 (CH), 129.70 (CH), 136.17 (C), 136.70 (CH), 139.13 (CH), 142. 69 (C), and 205.34 ppm (CO).
In the ^{1}H-nmr spectra, the protons of the methano bridge in the *endo* adducts exhibit a characteristic deshielding effect, probably due to the anisotropy of the close sulphinyl group. Compound **3** (*exo*): δ (CH_2) = 1.30 and 1.72 ppm; Compound **4** (*endo*): δ (CH_2) = 1.70 and 2.04 ppm; Compound **5** (*exo*): δ(CH_2) = 1.30 and 1.56 ppm; Compound **6** (*endo*): δ(CH_2) = 1.46 and 2.03 ppm.

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