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C2-SYMMETRIC BIS-SULFOXIDES AS CHIRAL LIGANDS IN METAL CATALYSED ASYMMETRIC DIELS-ALDER REACTIONS.

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Abstract: (S,S)-bis-p-Tolylsulfinylmethane, 1, and (S,S)-2,2-bis-(p-Tolylsulfinyl)propane, 2, were converted into their Fe(III) complexes I and II, respectively. These complexes were shown to be good chiral catalysts of the Diels-Alder reaction between 3-acryloyl-1,3-oxazolidin-2-one, 4, and cyclopentadiene. The good enantioselection observed (36 and 56%, respectively) can be explained by the model depicted in Figure 2.

Among the different chiral auxiliaries used in catalytic asymmetric synthesis,[1] those with a C_2 symmetry axis have received a special attention in the two last decades. The presence of a C_2 symmetry axis within the chiral auxiliary serves the very important function of reducing the number of competing diastereomeric transition states.[2] Besides the widely used bidentate phosphorous ligands,[3] bidentate ligands with two oxygen-donor atoms[4] constitute the second important class, due, in part, to the availability of C_2 symmetric species that can be derived from tartaric acid. Recently, the utilization of chiral bis-oxazolines, with two N-donor atoms, has permitted the development of powerful chiral catalysts of metal catalysed Diels-Alder[5] and cyclopropanation[6] reactions. Nevertheless, to our knowledge, no attention has been paid to bis-sulfoxides as bidentate ligands with two oxygen-donor atoms.

In this communication we present our preliminary results on the utilization of bis-sulfoxides with a C_2 symmetry axis (Fig. 1), as bidentate chiral controllers in a new catalytic system for the Diels-Alder reaction.[7] Such ligands are very attractive as a consequence of their ease of synthesis and their availability in the two enantiomeric forms from cheap starting materials.

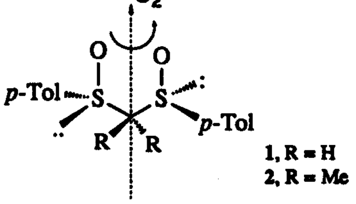
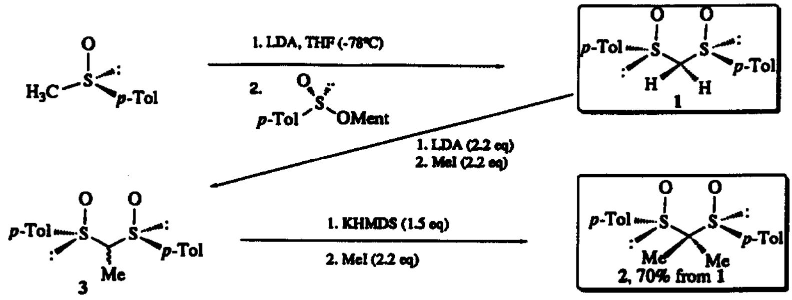


FIGURE 1

(*S*,*S*)-bis-*p*-Toylsulfinylmethane 1 has been easily obtained, in one step, from the known (*R*)-methyl *p*-tolyl sulfoxide[8] and the commercially available menthyl (*S*)-*p*-toluenesulfinate, as reported by Kuneida[9]

(Scheme 1). Since the menthyl (*R*)-*p*-toluenesulfinate is actually commercially available, the corresponding enantiomer of **1** is also accessible, in the same way.

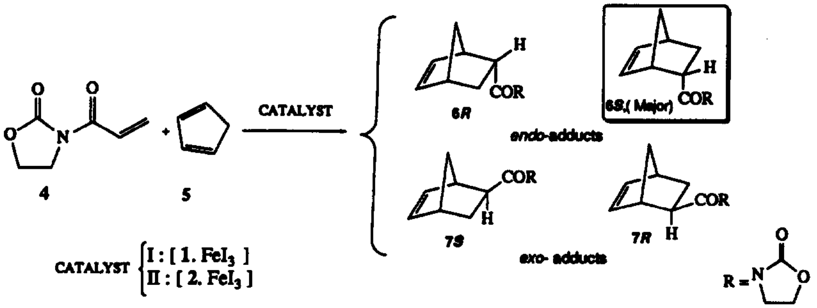
(*S*,*S*)-2,2-bis-(*p*-Tolylsulfinyl)propane **2** was obtained by dimethylation of **1** in two steps[10] (Scheme 1). Attempts to get **2** in one step by treatment of **1** with 2.2 eq. of base and 2.2 eq. of methyl iodide gave only the monomethylated product **3**.



SCHEME 1

The same synthetic route was followed for the synthesis of other chiral bis-sulfoxides with different R groups (R= Et, Bn, S-*p*-Tol, SBn). In all the studied cases, only the monosubstituted derivative was obtained. All the attempts to get the desidered C_2-symmetric bis-sulfoxides were unsuccessful. This must be due to steric and/or stereoelectronic effects.

For the studies of the catalytic Diels-Alder reaction, using the bis-sulfoxides **1** and **2** as chiral controller ligands, Fe(III) iodide was selected as the Lewis acid metal component, 3-acryloyl-1,3-oxazolidin-2-one **4** as a bidentate dienophile,[11] and cyclopentadiene **5** as the diene component (Scheme 2).



SCHEME 2

The catalysts I and II (Scheme 2) were prepared by stirring during 90 min. at 40ºC the corresponding bis-sulfoxide, **1** or **2**, with the appropriate amount of I_2 and Fe powder, previously heated for 1h. at 40ºC in CH_3CN. After removing the solvent at vacuo, a black viscous oil was obtained, supposed to be the complex [$1.FeI_3$] and [$2.FeI_3$], respectively. The reaction of 3-acryloyl-1,3-oxazolidin-2-one, **4**, and cyclopentadiene, **5**, in methylene chloride at -50ºC for 5 h., using 10 mol % of catalyst[12] afforded the Diels-Alder adduct in high yield. The results obtained for each catalyst are collected in Table 1.

Table 1 : Asymmetric induction obtained in metal catalysed Diels-Alder reactions, using bis-sulfoxide 1 and 2 as chiral controllers.

Bis-sulfoxide	Yield (%)	R	*Endo* : *Exo*	6*S* : 6*R*
1	74	H	95 : 5	68 :32
2	78	Me	96 : 4	78 :22

The diastereomeric excess was determined by ^{1}H NMR analysis of the mixture of reaction.[13] The major product was shown to be the 6*S* enantiomer, by measurement of the rotatory power and comparison with an authentic sample[5,11]. The 6*S*/6*R* ratio for the *endo* product was determined by HPLC analysis of the enantiomeric mixture, with a Diacel OD column using 5% isopropanol in hexane, which cleanly separates the enantiomers.[5] As can be seen in Table 1, in both cases the diastereoselection (*endo*/*exo*) is excellent, d.e.: 90-92%, and the enantioselection (6*S*/6*R*), which increased with the steric hinderence of R, goes from 36% (R=H) to 56% (R=Me).

The enantioselection observed in the Diels-Alder reaction described in this communication for catalysts I and II can be explained in terms of the transition state assembly represented in Figure 2. In this model, the bis-sulfoxide, 1 or 2, and the dienophile 4 are chelated to the metal with octahedral geometry, via the equatorial sites. The dienophile 4 chelates in the *s-cis* geometry, prior to the reaction with cyclopentadiene. Due to the steric hinderence of the *p*-tolyl groups, the cyclopentadiene approaches the chelated dienophile from the less hindered face, leading to the formation of the 6*S* adduct mainly.

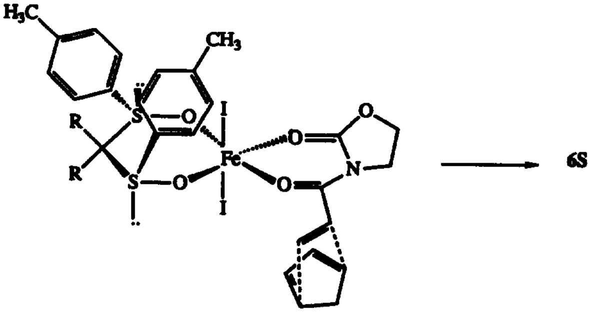


FIGURE 2

In conclusion, it has been shown for the first time that the bis-sulfoxides with a C_2 symmetry axis in their structure, are good chiral controller in metal catalysed asymmetric Diels-Alder reactions. These sulfoxides are readily available in the two enantiomeric forms and a simple column chromatography permits their recuperation and reuse, making this kind of C_2-symmetrical molecules highly attractive. Further works to optimize the enantiomeric excess and to apply these molecules to different types of catalytic asymmetric reactions are being pursued.

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10. Preparation of compound **2**: 0.34 mmol (0.1 g) of bis-sulfoxide **1** in THF (2 ml) are added, under argon, via canula over 0.74 mmol of freshly prepared solution of LDA in THF (3 ml) at -78ºC. After stirring 90 min, 0.74 mmol of MeI are added and the reaction is kept to warm to room temperature overnight. After the work up, the monomethylated product obtained, **3**, is placed in THF (5 ml) and treated with 0.5mmol of KHMDS (0.5 M solution) at -78ºC. The intense red solution obtained is stirred 1 h and then treated at 0ºC with 0.74 mmol of MeI. The TLC shows that the reaction has finished in 30 min. Purification by column chromatography gave 76 mg (70% yield, non optimized) of the desidered product **2**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.06 (s, 6H), 2.42 (s, 6H), 7.43 (AB system, $\Delta\upsilon$ = 42.6 Hz, J = 8.3 Hz, 8H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ 12.89, 21.49, 82.55, 126.55, 129.61, 135.27, 142.88 ppm.
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12. As it was reported by Corey in ref. 5, 1 eq. of iodine was added to the reaction mixture in order to accelerate the formation of the Diels-Alder adduct.
13. The ^{1}H NMR spectrum of the reaction mixture shows that in the *exo* isomer the olefinic protons appear together as a multiplet at δ 6.15 ppm , and they give two different signals (dd, J = 2.6, 5.6 Hz) at δ 5.84 and 6.23 ppm in the *endo* isomer.

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