Benzyl Methyl (*S*)-2-(*p*-Tolylsulfinyl)maleate: An Efficient Dienophile for the Enantioselective Synthesis of Cyclohexadienes

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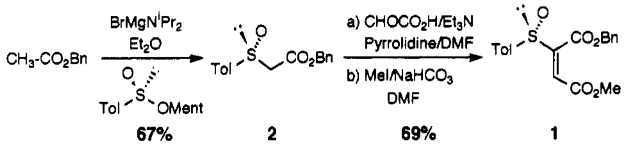
Summary: The new dienophile, benzyl methyl (*S*)-2-(*p*-tolylsulfinyl)maleate, readily prepared in two steps from benzyl acetate, reacts with a wide variety of 1,3-dienes, under catalysis by $TiCl_4$, in a very regioselective and stereoselective manner to give optically pure (ee >96%) 1,3- and/or 1,4-cyclohexadienedicarboxylate esters in very high yields.

The ability of the sulfinyl group to control the π-facial selectivity in the asymmetric Diels–Alder reaction has promoted the use of enantiomerically pure α,β-unsaturated sulfoxides as dienophiles. In order to take advantage of this ability it is essential that the vinyl sulfoxide possesses another electron-withdrawing functional group at the double bond which increases its dienophilic reactivity.[1] In this sense, significant contributions are the use of sulfinyl acrylates[2] and α-sulfinyl enones.[3] Usually, despite the second electron-withdrawing group at the double bond, the reactivity of these dienophiles is moderate, and this is probably the reason that the majority of the published studies deal only with the use of cyclopentadiene as diene. In order to overcome this important limitation the 2-sulfinylmaleates emerge as an interesting option.[4] Moreover, these dienophiles could act as interesting chiral equivalents of acetylenedicarboxylate esters in Diels–Alder reactions. In this paper we report that the readily available benzyl methyl (*S*)-2-(*p*-tolylsulfinyl)maleate (1) reacts, under catalysis by $TiCl_4$, with a wide variety of 1,3-dienes in a very regioselective and stereoselective manner to give in high yields 1,3- and/or 1,4-cyclohexadienedicarboxylate esters of very high enantiomeric purity.

The sulfinylmaleate 1 was prepared from benzyl acetate following the two-step sequence shown in Scheme I. The Andersen reaction of the magnesium enolate of benzyl acetate with (−)-(*S*)-menthyl *p*-toluenesulfinate gave 2 in 67% yield,[5] whose Knoevenagel condensation with glyoxylic acid in DMF at 0 °C, in the presence of pyrrolidine (0.35 equiv), followed by methylation with MeI afforded stereoselectively maleate 1 in 69% yield after chromatography[6] (ee >96%, determined by ^{1}H-NMR using Yb(hfc)$_3$).

Scheme I



After studying different Lewis acids,[7] we found that the Diels–Alder reactions of 1, catalyzed by $TiCl_4$ (1.2 equiv) in CH_2Cl_2, occured at low temperature (usually at −78 °C) with very high regioselectivity and stereoselectivity to give, with the majority of the dienes shown in Table I, only one adduct 3 which was characterized by ^{1}H-NMR. However, adducts 3 are not stable at rt due to their spontaneous sulfinyl elimination.[8] This elimination was complete after 24–48 h in CH_2Cl_2, affording 1,3-cyclohexadienes 4 and/or 1,4-cyclohexadienes 5. Compounds 4 and 5 were separated by chromatography,[9] and their ee's[10] were determined by ^{1}H-NMR using Pr(hfc)$_3$.

The most interesting findings deduced from the data of Table I[11] are the following: (a) The cycloadditions were completely regioselective with both 1-substituted and 2-substituted dienes (see entries c, d, f, and g), the process being controlled by the sulfinyl group. (b) The *endo* selectivity and π-facial selectivity must also be very high, as evidenced by the detection of only one adduct 3 by

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[1] For the activation of vinyl sulfoxides in Diels–Alder reactions by transformation into their alkoxysulfonium salts, see: Ronan, B., Kagan H. B. *Tetrahedron: Asymmetry* 1991, *2*, 75.

[2] For some recent references, see: (a) Takahashi, T.; Kotsubo, H.; Koizumi, T. *Tetrahedron: Asymmetry*, 1991, *2*, 1035. (b) Takahashi, T.; Kotsubo, H.; Iyobe, A.; Namiki T.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* 1990, 3065. (c) De Lucchi, O.; Buso, M.; Modena, G. *Tetrahedron Lett.* 1987, *28*, 107. (d) Koizumi, T.; Arai, Y.; Takayama, H.; Kuriyama, K.; Shiro, M. *Tetrahedron Lett.* 1987, *28*, 3689. (e) De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* 1986, *51*, 1457.

[3] (a) Alonso, I.; Carretero, J. C.; García Ruano, J. L. *Tetrahedron Lett.* 1989, *30*, 3853. (b) Maignan, C.; Guessous, A.; Rouessac, F. *Tetrahedron Lett.* 1986, *27*, 2603.

[4] For other previously reported 2-sulfinylmaleates, see: (a) Alonso, I.; Cid, M. B.; Carretero, J. C.; García Ruano, J. L.; Hoyos, M. A. *Tetrahedron: Asymmetry* 1991, *2*, 193. (b) Arai, Y.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.*, 1988, *29*, 6143. (c) Arai, Y.; Hayashi, K.; Matsui, M.; Koizumi, T.; Shiro, M.; Kuriyama, K. *J. Chem. Soc., Perkin Trans. 1* 1991, 1709. However, with these two dienophiles only the reactions with cyclopentadiene have been reported.

[5] Solladié, G. *Synthesis* 1981, 185.

[6] Data of compound 1: mp 66–69 °C; $[\alpha]^{20}_D = +158.6$ ($c = 1$, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.37 (s, 3H), 3.67 (s, 3H), 5.05 (s, 2H), 6.99 (s, 1H), 7.16–7.46 (m, 9H); ^{13}C-NMR ($CDCl_3$) δ 21.2, 52.2, 67.6 125.7, 125.9, 128.2, 128.3, 128.4, 129.8, 133.8, 136.9, 142.9, 150.4, 161.1, and 164.0 ppm. The same method has been previously used by us for the preparation of *tert*-butyl, methyl (*S*)-2-*p*-tolylsulfinylmaleate (see ref 4a). However, this dienophile is less reactive, less stereoselective, and less stable in the presence of Lewis acids than 1.

[7] $ZnBr_2$, ZnI_2, $LiClO_4$, $EtAlCl_2$, $BF_3{\cdot}Et_2O$, $MgBr_2{\cdot}Et_2O$, SiO_2, and $TiCl_4$ were used as catalysts.

[8] This spontaneous elimination of sulfenic acid to give 1,3-cyclohexadienes has also been observed in the Diels–Alder reaction of acyclic dienes with racemic α-phenylsulfinyl α,β-unsaturated ketones (Alexandre, C.; Belkadi, O.; Maignan, C. *J. Chem. Res., Synop.* 1992, 48).

[9] Cyclohexadienes 4 and 5 described in this paper can be stored unaltered for months in the refrigerator (at −20 °C). Compounds 5e, 5f, and 5g easily give the aromatization product. Therefore, their isolation and purification must be quickly carried out at low temperature.

[10] For the study of the ee's, all compounds 4 and 5 have also been prepared in racemic form from (±)-1, which was prepared according to Scheme I using (±)-methyl *p*-toluenesulfinate.

[11] **General Procedure.** $TiCl_4$ (0.67 mmol, 1.2 equiv from a solution 1.0 M in CH_2Cl_2) was added dropwise, under argon atmosphere, to a solution of dienophile 1 (200 mg, 0.56 mmol, 1.0 equiv) in 2.8 mL of CH_2Cl_2 at −78 °C. The mixture was stirred for 10 min, and then 6 equiv of the diene was added. Stirring was continued until dienophile disappeared by TLC (the reaction time is indicated in Table I). Then, 10% $NaHCO_3$ (10 mL) was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were washed with water (5 mL), dried ($MgSO_4$), and carefully evaporated (without heating). The adduct 3 was readily analyzed by ^{1}H NMR, and its solution in CH_2Cl_2 (5 mL) was allowed to stand at rt until complete sulfinyl elimination (24–48 h). The solvent was evaporated and the cyclohexadienes 4 and/or 5 were purified and separated by flash chromatography.

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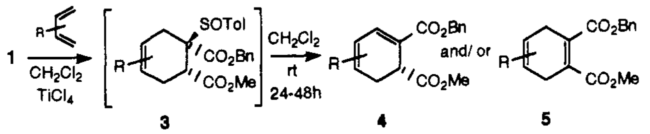
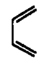
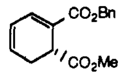
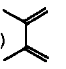
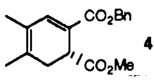
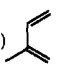
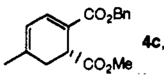
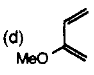
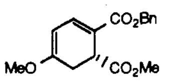
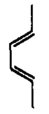
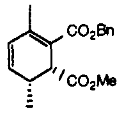
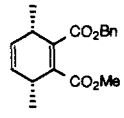
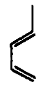
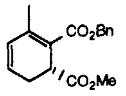
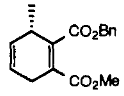
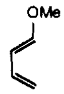
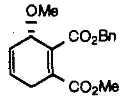
Table I. Diels–Alder Reactions of 1[11]

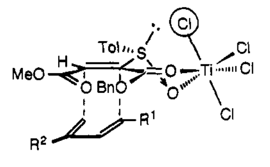


diene	cycloaddition condns	products yield,[a] ee
(a) 	-78°C, 90h	 4a, 83%, >96%
(b) 	-78°C, 28h	 4b, 66%, >96%
(c) 	-78°C, 28h	 4c, 91%, >96%
(d) 	Eu(fod)$_3$[b] 0°C, 96h	 4d, 87%, 83%
(e) 	-78°C, 22h	 4e, 64%, >96% +  5e, 27%, [c]
(f) 	-78°C, 24h	 4f, 31%, >96% +  5f, 41%, >96%
(g) 	Eu(fod)$_3$[b] 0°C, 3h	5g, 67%, >96% 

[a] In pure product after chromatography. [b] Diene polimerizes in the presence of $TiCl_4$. [c] The ee could not be determined.

^{1}H-NMR. Accordingly, cyclohexadienes 4 and 5 show very high ee's (usually >96%). (c) Butadiene and all the 2-substituted dienes used gave exclusively 1,3-dienes 4 (entries a–d), whereas some 1-substituted dienes afforded a mixture of 1,3- and 1,4-dienes (entries e and f). (d) Alkoxy dienes are not compatible with the presence of $TiCl_4$ due to their rapid polymerization. In these cases satisfactory results were obtained using Eu(fod)$_3$ (1.2 equiv) as catalyst[12] (entries d and g).

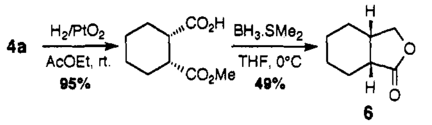
The stereochemical assignment of the products shown in Table I has been unequivocally established in the case of 4a by chemical correlation with the previously reported lactone 6[13] (Scheme II). We assume for the other products 4 and 5 the same relative configurations, based on the sign of their $[\alpha]^{20}{}_D$ values, the homogeneous behavior of their chemical shifts in the presence of Pr(hfc)$_3$ compared to the racemic ones,[10] and mechanistic considerations. These stereochemical results can be explained by assuming an *endo* approach of the diene to the less hindered face of the $TiCl_4$-complexed vinyl sulfoxide 1 (opposite to the apical chlorine atom) on its most stable *s-trans* conformation[14] (Figure 1).



endo-approach

Figure 1.

Scheme II



In summary, it has been shown that the Diels–Alder reaction of 1 is an efficient method for the preparation of a wide variety of cyclohexadienedicarboxylate esters of a very high enantiomeric purity. Currently, we are applying this reaction to the synthesis of various natural products.

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Supplementary Material Available: Experimental procedures and characterization data for all new compounds and ^{1}H NMR spectra of compounds 4 and 5 (17 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[12] With some 1-substituted dienes, such as 2,4-hexadiene or piperilene, the ee's of 4 or 5 using Eu(fod)$_3$ as catalyst are lower than with $TiCl_4$.

[13] Lactone 6: $[\alpha]^{20}{}_D = -49.3$ ($c = 0.48$, $CHCl_3$) (lit. $[\alpha]^{20}{}_D = +48.8$ (for (+)-6, $c = 0.5$, $CHCl_3$)): (a) Toone, E. J.; Jones, J. B. *Tetrahedron: Asymmetry* **1991**, *2*, 207. (b) Jakovac, I. J.; Goodbrand, H. B.; Lok, K. P.; Jones, J. B. *J. Am. Chem. Soc.* **1982**, *104*, 4659.

[14] In α-sulfinyl acrylates and α-sulfinyl enones it has been proposed that whereas in the absence of Lewis acids the *s-cis* conformation is the most stable due to dipole–dipole repulsion and steric factors, in the presence of Lewis acids the conformational equilibrium shifts to the *s-trans* conformation due to its strong stabilization by chelation (see refs 2d, 3, and 4).