

A NEW APPROACH TO THE ASYMMETRIC CYCLOPROPANATION VIA A CHIRAL SULFINYL GROUP

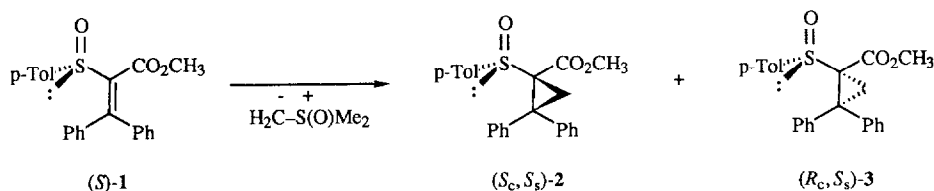
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Summary: High stereoselectivity and high yield are observed in the Michael addition of dimethyl sulfoxonium methylide to an optically pure methyl α -(*p*-tolylsulfinyl) acrylate. A novel route to the asymmetric synthesis of electrophilic cyclopropanes.

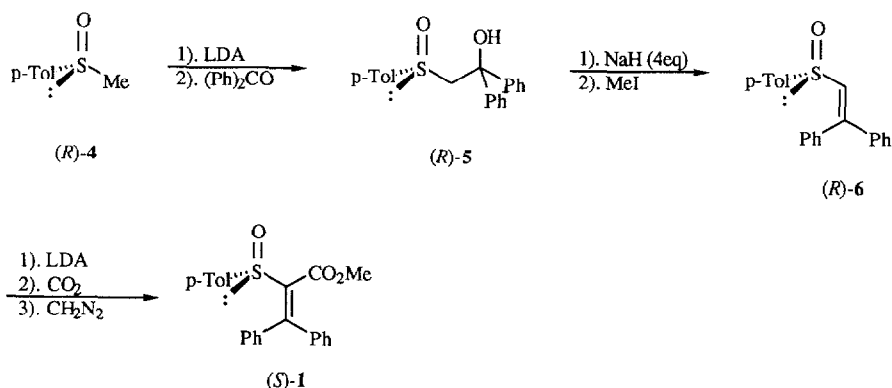
Several methods have been reported¹ for the cyclopropanation of activated-electron deficient alkenes via Michael addition of ylide type carbanions involving the formation of zwitterionic intermediates. However, few methods are available for the application of this reaction in asymmetric synthesis of electrophilic cyclopropane derivatives². The only known method employs alkenes complexed with a chiral iron carbonyl³ which require resolution via an oxazolidine.

Chiral vinyl sulfoxides have been employed in asymmetric Diels-Alder reactions⁴ and as Michael acceptors of a variety of nucleophiles⁵. We describe here an approach to asymmetric cyclopropanation involving the use of a chiral vinyl sulfoxide as a Michael acceptor of dimethyl sulfoxonium methylide. Initially we selected as a target a chiral electrophilic cyclopropane disubstituted by phenyl groups. This type of system has been used in numerous mechanistic studies reported by Walborsky et al⁶.



The starting (*R*)-(+)-methyl *p*-tolylsulfoxide (**4**) was prepared from (-)-menthyl-(*S*)-*p*-toluenesulfinate according to the method reported by Solladié et al⁷. The addition of benzophenone to the chiral carbanion of **4** afforded the hydroxysulfoxide **5** in 88% yield ($[\alpha]_{\text{Hg}} +86.3^\circ$, *c*, 1.14, CHCl_3). Treatment of **5** with sodium hydride followed by methyl iodide in THF produced the desired vinyl sulfoxide **6** in 92% yield ($[\alpha]_{\text{Hg}} -260^\circ$, *c*, 0.44, CHCl_3). The conversion of the vinyl sulfoxide **6** to ester **1** was achieved by α -lithiation (LDA, THF, -78°C) followed by carboxylation (CO_2 , -78°C)⁸ and esterification with diazomethane to give the optically pure methyl α -(*p*-tolylsulfinyl) acrylate **1** in 81% yield from **6** ($[\alpha]_{\text{Hg}} +45^\circ$, *c*, 1, acetone).

Cyclopropanation was carried out in DMSO at ambient temperature by treatment of **1** with an excess of dimethyloxosulfonium methylide (3 eq), freshly prepared from trimethyloxosulfonium iodide and sodium hydride, to produce a mixture of two diastereoisomers **2** and **3** in 96% yield and a ratio of 1 : 5.9 respectively. The diastereoselectivity of this reaction was determined by ^1H NMR from the signals corresponding to the cyclopropyl protons. A simple flash chromatography on silica gel afforded **3** in 82% yield and d.e. > 98% ($[\alpha]_{\text{Hg}}^{+48^\circ}$, c, 0.5, acetone)⁹.



In order to corroborate the stereochemistry of this reaction, an X-ray analysis was carried out on **3**. A perspective view showing the absolute configuration of **3** is given in Figure 1.

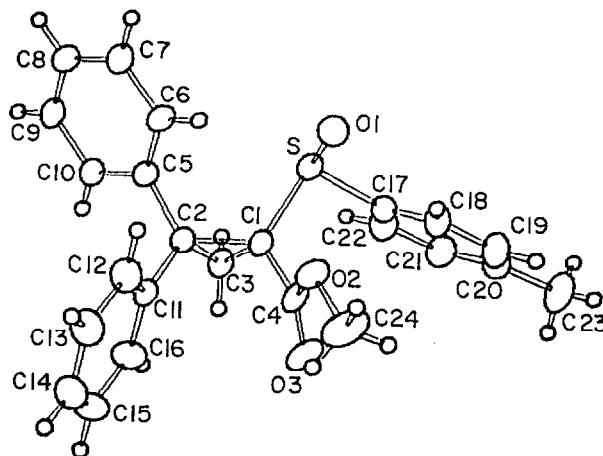
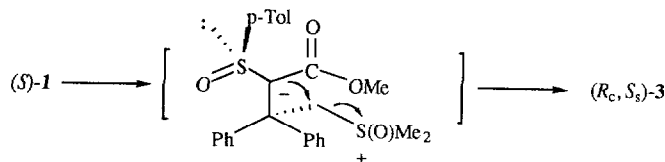


Figure 1. ORTEP plot of **3**.

From this structure it may be inferred that the transition state for this cyclopropanation involved a non-chelate model in which the bond dipoles of the *p*-tolylsulfinyl and the carbonyl groups are oriented in opposite directions^{5e,11}. The 1-3 elimination occurred preferentially from the lone pair side of the *p*-toluenesulfinyl, leading to the formation of the major diastereoisomer.



This is the first example of asymmetric cyclopropanation using a chiral vinyl sulfoxide as a Michael acceptor of dimethyl sulfoxonium methylide. Work is in progress to apply this reaction in synthesis of natural product intermediates.

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9. **Cyclopropanation of 1** : A solution of dimethyloxosulfonium methylide in 30 mL of DMSO was prepared under argon, from trimethyloxosulfonium iodide (9.6 mmol) and NaH (60% dispersion in oil, 9.6 mmol) at rt. After stirring for 90 min (the evolution of hydrogen ceased) the solution of ylide was added dropwise to a solution of sulfoxide **1** (3.2 mmol) in 25 mL of dimethyl sulfoxide over a 30 min period. The reaction mixture was stirred at rt for 14 hours, poured onto an ice-water mixture, and extracted twice with ether. The ether layers were washed twice with water, dried over anhydrous $MgSO_4$ and evaporated *in vacuo* to give a crude cyclopropyl sulfoxide as a white solid. Flash chromatography (silica, ethyl acetate-n-hexane (25:75)) gave 0.17 g (14%) of **2** and 1.02g (82%) of **3**; TLC (ethyl acetate-n-hexane (4:6)) Rf 0.52 and 0.37.

2. mp 202-203°C; 1H NMR δ 2.3 (A part of AB system, 1H, J_{AB} =6.3 Hz), 2.37 (s, 3H, CH_3 p-tol), 2.78 (B part of AB, 1H, J_{AB} =6.3Hz), 3.2 (s, 3H, CH_3 ester), 7.18-7.62 (m, 14H, aromatics).

3. mp 227-228°C; $[\alpha]_{Hg}^{25} +48^\circ$ (c 0.44, acetone); IR ($CHCl_3$) 3000, 1720, 1225, 1210 cm^{-1} ; 1H NMR δ 2.24 (A part of AB system, 1H, J_{AB} =5.8Hz), 2.37 (s, 3H, CH_3 p-tol), 2.5 (B part of AB system, 1H, J =5.8Hz), 3.4 (s, 3H, CH_3 p-tol), 7.15-7.8 (m, 14H, aromatics).

Anal. Calcd for $C_{24}H_{22}O_3S$: C, 73.82; H, 5.68. Found C, 73.68; H, 5.69.

10. **X-ray Analysis of (3)**. Single crystals were grown by slow cooling of a methanol solution of the compound. The crystals were monoclinic, space group $P2_1$ with $a = 1.861(2)$, $b = 6.108(1)$, $c = 14.644(8)$ Å and $d_{calcd} = 1.257$ g cm^{-3} for $Z = 2$ ($M_r = 390.51$). Tables 1-4 listing summary of data, bond angles, bond lengths and positional and thermal parameters including their estimated standard deviations. Ordering information is given on any current masthead page.

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