Pergamon

Tetrahedron: Asymmetry, Vol. 7, No. 1, pp. 57-60, 1996

0957-4166/96 $15.00 + 0.00

0957-4166(95)00420-3

# Asymmetric Diels-Alder Reaction of α-Sulfinylacrylate Derived from (1*R*, 2*S*, 3*R*)-3-Mercaptocamphan-2-ol

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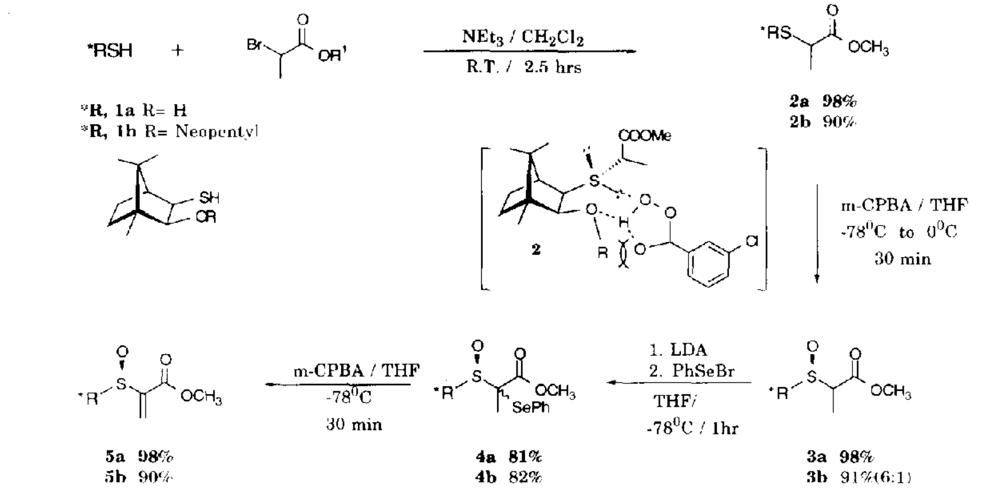
**Abstract :** The Diels-Alder reaction of cyclopentadiene with a new chiral α-sulfinylacrylate, which was prepared from MerCO[(1*R*, 2*S*, 3*R*)-3-mercaptocamphan-2-ol] at -78°C in the presence of $ZnCl_2$ produced an endo-cycloadduct with 99.4% d.e. in 84% yield.

The superior facial selectivity of the chiral vinyl sulfoxides as dienophiles has received much attention recently.[1] These compounds are expected to induce chirality more efficiently than the corresponding acrylates with optically active alcohols since their stereogenic centers are adjacent to the reaction centers. While in the latter case, the stereogenic centers involved are at least three bonds away.[2] The earlier studies indicate that vinyl sulfoxides require harsher reaction conditions than acrylates in cycloaddition and consequently lead to lower stereoselectivity.[3] Koizumi and De Lucchi have demonstrated elegantly the use of the combination of both chiral auxiliaries, alcohols and sulfoxides, to produce several chiral β-sulfinylacrylates with very good diastereoselectivity.[4] On the other hand, the chiral α-sulfinylacrylate has been rarely discussed in the literature.[5] In this paper we report a new chiral α-sulfinylacrylate which was prepared from MerCO[(1*R*, 2*S*, 3*R*)-3-mercaptocamphan-2-ol **1a**].[6] The dienoplile of this type gave very high diastereoselectivity and was found to have higher reactivity than the corresponding β-sulfinylacrylates in the cycloaddition with cyclopentadiene. We assume that the later property may be due to the coherent polarization effect of the sulfinyl and carboxyl group on the same olefinic carbon.[7]

Starting from the chiral auxiliary **1a** and **1b**, the desired dienophiles **5a** and **5b** were prepared in a few simple steps. Thus, the coupling of thiol **1a** or **1b** with methyl α-bromopropionate was aided by 1 equivalent of triethylamine in dichloromethane at ambient temperature, and the methyl α-thiopropionate **2a** or **2b** were isolated in 98% and 90% yields, respectively. The oxidation of α-thioester **2a** by *m*-CPBA generated essentially a single sulfoxide **3a** in nearly quantitative yield. No trace of the other epimeric sulfoxide was detected by 300MHz $^1H$ NMR spectroscopy. Previously De Lucchi reported that the diastereoselectivity of the sulfide oxidation by *m*-CPBA in 2-hydroxy-10-mercaptocamphor based acrylate gave 22% - 92% d.e..[4b,4d] Our result suggested that the inducing effect of the 2-hydroxy group in the oxidation of **2a** was even better than that of De Lucchi's oxidation.[4b,8] On the other hand, similar oxidation of α-sulfenylester **2b** gave a 6:1 diastereomeric mixture of sulfoxides **3b** with the *R*-form as the major isomer. This observation further supported our proposed transition state 2 in which the *m*-CPBA was strongly chelated with the 2-hydroxyl group. The bulky neopentyl group destabilized the transition state **2** and thus lowered the diastereoselectivity of the oxidation. The diastereomerically pure α-sulfinylester **3a** was then treated sequentially with lithium diisopropylamide and phenylselenyl bromide, followed by *m*-CPBA to give the α-sulfinylacrylates **5a** in 80%

overall yield. A similar reaction was carried out on the *R*-isomer of α-sulfinylester **3b**, and α-sulfinylacrylates **5b** was obtained in 74% yield, as shown in scheme 1.

**Scheme 1:**



The Diels-Alder reactions of α-sulfinylacrylate **5a** and **5b** with cyclopentadiene were carried in dichloromethane at a variety of temperatures. The results collected in Table 1 indicated that both of **5a** and **5b** produced the corresponding endo-(*Si*)-**7** as the major cycloadducts (entry 1-4). According to the preceding examples in the literature, the α-sulfinylacrylate preferred to adapt conformation **5X** due to dipole-dipole interactions between carbonyl and sulfinyl groups.[4] The *Re*-face approach of the cyclopentadiene was somewhat hindered by the 7-methyl group of the camphor skeleton, which was probably the origin of the diastereoselectivity. Meanwhile, the carbonyl generally had a stronger endo-directing effect over the sulfinyl groups.[5a] Therefore, the endo-(*Si*)-**7** was produced predominately in both cases, and the temperature seemed to have no or little effect on the product distributions(Scheme 2).

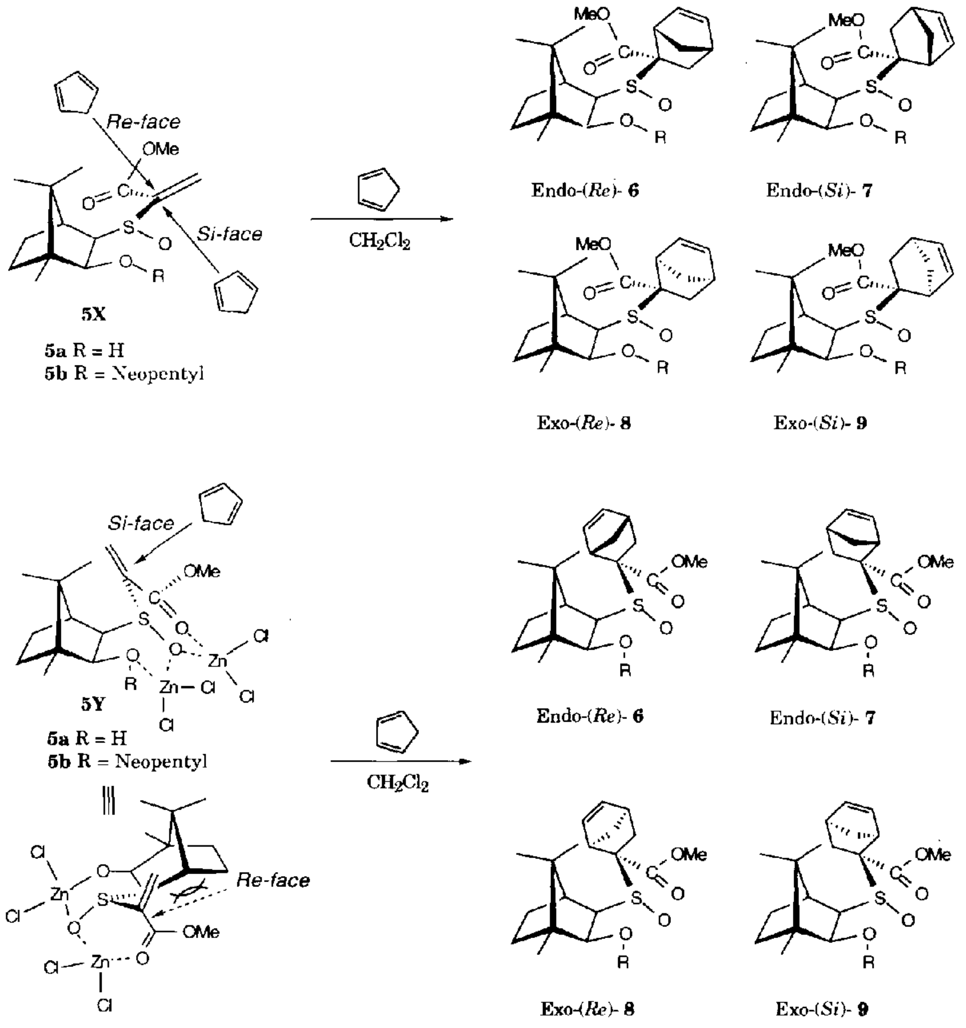
**Table 1:** Cycloaddition of α-sulfinylacrylate **5** with cyclopentadiene

| Entry | Dieneophiles | Catalyst[a] | Temperature | Cycloadduct Yield,[b] % | Ratio[c,d] | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | **6** | **7** | **8** | **9** |
| 1 | **5a** | - | ambient | 81 | 27 | 51 | 16 | 6 |
| 2 | **5a** | - | 0°C | 94 | 27 | 51 | 16 | 6 |
| 3 | **5b** | - | ambient | 91 | 18 | 60 | 16 | 6 |
| 4 | **5b** | - | 0°C | 92 | 20 | 60 | 15 | 5 |
| 5 | **5a** | $ZnCl_2$ | ambient | 88 | 0 | 88 | 0 | 12 |
| 6 | **5a** | $ZnCl_2$ | 0°C | 84 | 0 | 92 | 0 | 8 |
| 7 | **5a** | $ZnCl_2$ | -78°C | 84 | 0 | 99.7 | 0 | 0.3 |
| 8 | **5b** | $ZnCl_2$ | ambient | 90 | 0 | 76 | 0 | 24 |
| 9 | **5b** | $ZnCl_2$ | 0°C | 83 | 0 | 81 | 0 | 19 |
| 10 | **5b** | $ZnCl_2$ | -78°C | 85 | 0 | 90 | 0 | 10 |

[a] Two equivalents of the anhydrous $ZnCl_2$ was used. [b] The reaction yields were based on the isolation of the products after purification. [c] The diastereomeric ratios were determined by HPLC analysis. [d] The sequence number of the products were corresponded to their retention time in HPLC column, i.e., compound **6** came out first and so forth.

On the contrary, the presence of a Lewis acid catalyst, $ZnCl_2$, the diastereoselectivity was improved greatly as shown in entry 5-10. The *Re*-face approach was totally blocked by the camphor backbone as illustrated in the metal chelated conformer **5Y**, which diminished the *Re*-face cycloadducts **6** and **8**. Meanwhile, the temperature effect was very significant at -78°C, the endo-(*Si*)-**7a** was nearly the only product obtained.[9,10,11]

**Scheme 2:**



On the other hand, the diastereoselectivity was reduced when the 2-hydroxyl group in dienophile **5a** was replaced by the bulky 2-neopentoxy group in **5b**. The chelation of $ZnCl_2$ with conformer **5Y** formed a rigid network, which led to the high facial selectivity for the cycloaddition. However, the steric bulkiness of the 2-neopentoxy group disturbed such an arrangement and thus lowered the stereoselectivity (entry 8-10).

In summary, this paper reports a new α-sulfinylacrylate **5a** which has the highest diastereoselectivity toward the Diels-Alder reaction ever reported.[5] Meanwhile, the study of the cycloaddition of α-sulfinylacrylate **5b** helps us to understand the importance of the neighbouring hydroxyl group to the stereoselectivity.[5b,5d,8] The same principle may also apply to the oxidation of the sulfide **5b**.[8] In addition, we found a significant temperature effect for the Lewis acid catalyzed cycloaddition while the temperature has little influence in the absence of the catalyst. Further applications derived from the information provided in this study, such as a chiral sulfinyl enophile, are currently under investigation.

**Acknowledgment:** We thank the National Science Council of the Republic of China for financial support under grant No. NSC-84-2113-M005-003 and Professor Albert S. C. Chan for his helpful discussion.

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9. The X-ray crystallographic studies of the cycloadducts of endo-(*Re*)-**6a** and exo-(*Si*)-**9a** supported the stereochemistry that we proposed. Based on the precedent and our hypothesis, exo-(*Re*)-**8a** was the least possible product which could easily be differentiated from the highly predominated cycloadduct **7a**.
10. Crystal data of endo-(*Re*)-**6a** and exo-(*Si*)-**9a** are supplied as supplementary material. The atomic coordinates have been deposited in Cambridge Crystallographic Data Centre.
11. Endo-(*Si*)-**7a:** $^1$H NMR(300MHz, $CDCl_3$) δ 0.83(s, 3H), 0.99(s, 3H), 0.80-1.25(m, 2H, $CH_2$), 1.25(s, 3H), 1.45-1.58(m, 2H), 1.70-2.00(m, 4H), 1.76(d, J=3.9Hz, 1H), 2.74(d, J=7.2Hz, 1H), 3.09(s, 1H), 3.18(br s, 1H), 3.73(s, 1H), 3.78(s, 3H) 4.07(d, J=7.2Hz, 1H), 6.04(dd, J=5.4, 3.0Hz, 1H), 6.36(dd, J=5.4, 3.0Hz, 1H); $^{13}$C NMR(75.4MHz, $CDCl_3$) δ 11.31, 21.14, 22.31, 28.95, 32.99, 33.76, 43.99, 46.32, 47.27, 47.65, 48.41, 49.72, 52.47, 72.03, 72.99, 81.00, 133.40, 141.20, 170.28.

*(**Received in Japan** 13 **November** 1995)*