Pergamon

Tetrahedron Letters, Vol. 37, No. 26, pp. 4537-4540, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00897-0

The Study of Lewis Acid Effect on Asymmetric Diels-Alder Reactions of New 2-Sulfinylbutadienes Derived from (1*R*, 2*S*, 3*R*)-3-Mercaptocamphan-2-ol

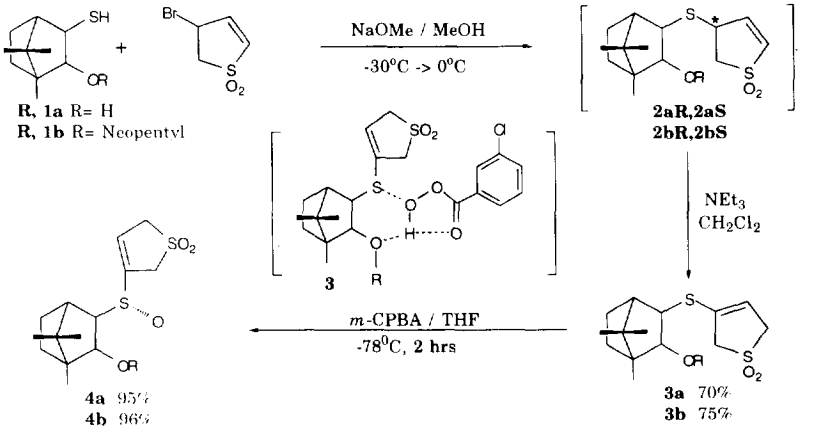
Teng-Kuei Yang,*[a] Han-Yang Chu,[a] Dong-Sheng Lee,[a,b] Yao-Zhong Jiang,[b] Ta-Shue Chou[c]

[a]Department of Chemistry, National Chung-Hsing University, Taichung, Taiwan 400, Republic of China
[b]The Union Laboratory of Asymmetric Synthesis, Academia Sinica, Chengdu 610015, China
[c]Institute of Chemistry, Academia Sinica, Taipei, Taiwan 100, Republic of China

Abstract : The Diels-Alder reactions of N-phenylmaleimide and new chiral 2-sulfinylbutadienes, which were prepared from MerCO[(1*R*, 2*S*, 3*R*)-3-mercaptocamphan-2-ol], produced cycloadducts up to 99% d.e. in the presence of $LiClO_4$ at ambient temperature. On the other hand, we found the facial selectivity of the cycloaddtion changed greatly among various Lewis acids.

The feature of Diels-Alder reaction stereospecifically creating up to four stereogenic centers in a single process has made it become a popular subject in field of asymmetric synthesis.[1] Because the success of such cycloaddition relied on the choice of highly diastereoselective chiral dienophiles and enophiles, fruitful applications of chiral dienophiles were achieved during the past decade.[2,3,4] However, the developments of enantiopure dienes(enophiles) received much less attention.[5,6,7] This was partly due to the instability for most dienes which made them difficult to be synthesized. In contrast, this problem could be overcome by attaching the chiral auxiliaries to the stable 3-sulfolene which generated chiral dienes during the cycloadditions.[8] Recently, we reported the use of MerCO, (1*R*, 2*S*, 3*R*)-3-mercaptocamphan-2-ol, as the chiral source of chiral dienophiles for controlling the asymmetric induction in the Diels-Alder reaction.[9] This paper reported the Diels-Alder reactions of N-phenylmaleimide and new MerCO based chiral 2-sulfinylbutadienes, which produced excellent yields as well as diastereoselectivities of the corresponding cycloadducts. More importantly, we found the stereoselectivities of these cycloadditions were greatly influenced by the size of Lewis acids catalysts. Actually, this significant phenomenon was rarely mentioned and rationalized in the previous literatures.[7]

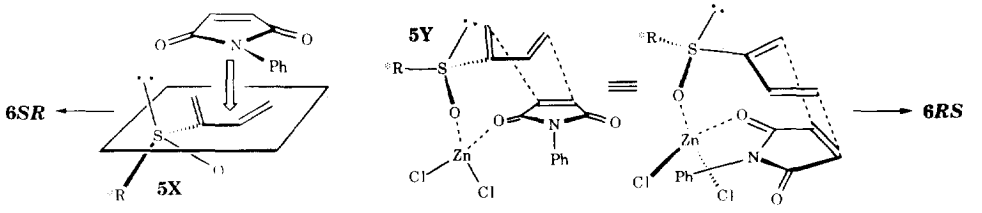
Scheme 1:



Our strategy for the preparation of the sulfolene **4a** and **4b**, the precursors of diene **5a** and **5b**, began with the coupling of thiol **1a** or **1b**[9] with 4-bromo-2-sulfolene in the presence of two equivalents of sodium

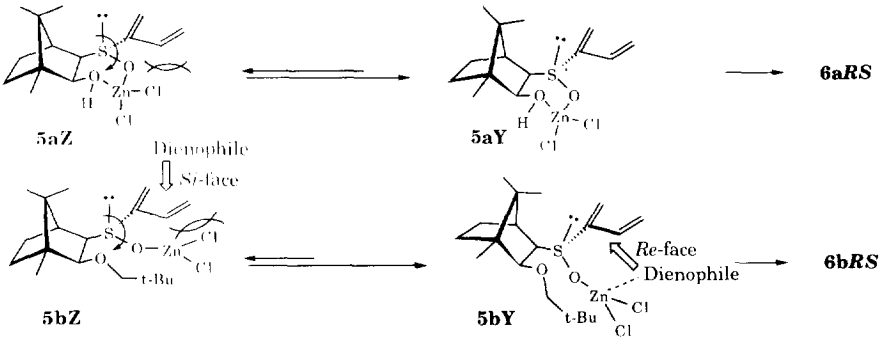
methoxide. The reactions were carried out in methanol initially at -30 °C, and the reaction temperature was gradually raised to ambient temperature. The rearrangement of the diastereomeric 4-mercapto-2-sulfolene **2a** or **2b**, upon addition of triethylamine, produced 4-mercapto-3-sulfolene **3a** or **3b** in 70% and 75% yields, respectively.[8a] The oxidation of 4-mercapto-3-sulfolene **3a** by *m*-CPBA generated essentially a single isomer, 4-sulfinyl-3-sulfolene **4a**, in 95% yield. No trace of the other diastereomeric sulfoxide of **4a** was detected by 300MHz ^{1}H NMR spectroscopy. This result suggested that the 2-hydroxy group had a strong directing effect in the oxidation of **3a**, as we observed in other related oxidation reactions.[4,10] On the other hand, similar oxidation of 4-mercapto-3-sulfolene **3b** gave exclusively sulfoxide **4b** in 96% yield with the *R*-configuration at the sulfur chiral center, as shown in Scheme 1.

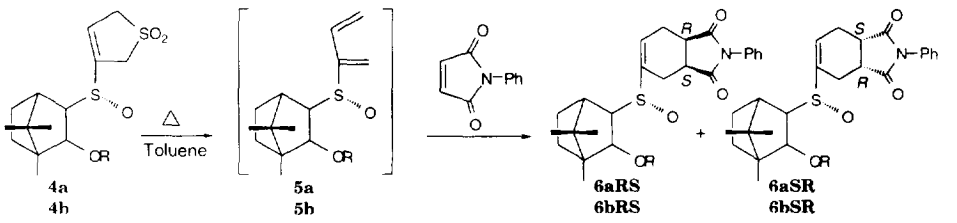
Figure 1:



Due to the potential instabilities of the dienes **5**, they were *in situ* generated from 4-sulfinyl-3-sulfolene **4** in refluxing toluene and used directly for cycloaddition at the designated reaction condition. Table 1 summarized the results of the Diels-Alder reactions of the dienes **5** and N-phenylmaleimide under a variety of conditions. The data in entries 1-2 and 12-14 of Table 1 indicated that N-phenylmaleimide preferred to approach the *Si*-face of the 2-sulfinylbutadiene **5X**, thus the cycloadducts **6a*SR*** and **6b*SR*** were formed as the major diastereomers from dienes **5a** and **5b**, respectively. These results could be explained by the π-facial stereoselection of the electrophilic N-phenylmaleimide preferred to add to the electron-rich face of the nucleophilic dienes **5X**.[11] On the contrary, the presence of a Lewis acid gradually turned the diastereoselectivity around depending on the sizes of the catalysts. (Figure 1) The most significant effect was observed in entries 17, 19, and 20 in which the use of $ZnCl_2$, $ZnBr_2$, and ZnI_2 as catalyst gave 72%, 82%, and 90% diastereoselectivity for **6b*SR***, respectively. Meanwhile, the same diastereoselective sequence of **6a*SR*** was observed for the cycloaddition of diene **5a**. (Entry 7, 9, and 10) The stereochemistry of the cycloadduct **6a*SR*** was supported the X-ray crystallography. The structures of the other cycloadducts were deduced from the ^{1}H NMR spectroscopy by comparing the chemical shifts of the hydrogen atoms on C-4 of the camphor skeleton.[12]

Figure 2:





4a **4b** **5a** **5b** **6aRS** **6bRS** **6aSR** **6bSR**

Table 1: Cycloaddition of 2-sulfinylsulfolenes **4** with N-phenylmaleimide

Entry	Sulfolenes	Catalyst[a]	Temperature (time)	Solvent	Cycloadduct Yield,[b] %	Ratio[c] **6*RS*** : **6*SR***
1	**4a**	-	ambient (72hrs)	Toluene	78	20 : 80
2	**4a**	-	reflux (12hrs)	Toluene	95	23 : 77
3	**4a**	$AlCl_3$	ambient (24hrs)	CH_2Cl_2	84	49 : 51
4	**4a**	$TiCl_4$	ambient (24hrs)	CH_2Cl_2	78	60 : 40
5	**4a**	M.S.(3A)	ambient (24hrs)	CH_2Cl_2	80	75 : 25
6	**4a**	M.S.(4A)	ambient (24hrs)	CH_2Cl_2	77	81 : 19
7	**4a**	$ZnCl_2$	ambient (24hrs)	CH_2Cl_2	78	70 : 30
8	**4a**	$MgBr_2$	ambient (24hrs)	CH_2Cl_2	84	74 : 26
9	**4a**	$ZnBr_2$	ambient (24hrs)	CH_2Cl_2	88	76 : 24
10	**4a**	ZnI_2	ambient (24hrs)	CH_2Cl_2	82	82 : 18
11	**4a**	$LiClO_4$	ambient (24hrs)	CH_2Cl_2	88	90 : 10
12	**4b**	-	ambient (72hrs)	Toluene	78	22 : 78
13	**4b**	-	ambient (72hrs)	CH_2Cl_2	85	22 : 78
14	**4b**	-	reflux (12hrs)	Toluene	93	25 : 75
15	**4b**	M.S.(3A)	ambient (24hrs)	CH_2Cl_2	83	72 : 28
16	**4b**	M.S.(4A)	ambient (24hrs)	CH_2Cl_2	80	86 : 14
17	**4b**	$ZnCl_2$	ambient (24hrs),	CH_2Cl_2	84	86 : 14
18	**4b**	$MgBr_2$	ambient (24hrs)	CH_2Cl_2	85	88 : 12
19	**4b**	$ZnBr_2$	ambient (24hrs)	CH_2Cl_2	86	91 : 9
20	**4b**	ZnI_2	ambient (24hrs)	CH_2Cl_2	87	95 : 5
21	**4b**	$LiClO_4$	ambient (24hrs)	CH_2Cl_2	86	>99 : 1

[a] Two equivalents of the Lewis acids were used in general. [b] The reaction yields were based on the isolation of the products after purification. [c] The diastereomeric ratios were determined by HPLC analysis.

In Figure 2, we proposed that a larger Lewis acid reinforced the steric repulsion between the Lewis acid and the diene moiety, which twisted C-S bond clockwisely. Therefore, the conformer **5bY** would be preferred in the equilibrium between the conformer **5bZ** and **5bY**. As a result, the sulfinyl oxygen would be further downward from the plane of the diene moiety, which provided more space in the *Re*-face of the diene for the incoming dienophlie through the chelation of the Lewis acids. According to this hypothesis, the diastereoselectivity would be increased along with the size-increment of the catalyst. In fact, the best result was observed when $LiClO_4$ was used as the catalyst, where the cycloadduct **6b*SR*** was obtained almost exclusively.[14] (Entry 21) On the other hand, the metallic ion chelation to both of the sulfinyl and the 2-hydroxy oxygens tended to pull the Lewis acid away from the diene moiety. The lower stereoselectivity of the diene **5a** (as compared to **5b**) may be due to the less difference between the conformer **5aZ** and **5aY**, or poor chelation of the Lewis acid and the dienophile.

In summary, the two new chiral 2-sulfinyldiene **5a** and **5b** gave moderate diastereoselectivity in the cycloaddition with N-phenylmaleimide. However, excellent diastereoselectivity was achieved when a proper catalyst was used. Meanwhile, we found a significant steric effect on stereoselectivity related closely with the sizes of the Lewis acids, and it was rationalized as a result of the equilibrium between the conformer **5Z** and **5Y**. We believed that the information provided in this paper is very useful for the selection of proper conditions for the asymmetric cycloaddition of the chiral sulfinyldiene system.

Acknowledgment: We thank the National Science Council of the Republic of China for the financial support under grant No. NSC-85-2113-M005-007, and Professor Y. Yamamoto for his helpful discussion.

REFERENCES AND NOTES:

1. Oppolzer, W. *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 876.
2. Barbachyn, M. R.; Johnson, C. R. in "Asymmetric Synthesis" Morrison, J. D.; Ed.; Academic press: New York, **1984**, Vol. 3, Chap. 7.
3. For a general review of sulfur directing olefins in cycloaddition please see: De Lucchi, O.; Pasquato, L. *Tetrahedron*, **1988**, *44*, 6755-6794.
4. For chiral sulfinyl acrylates please see: Yang, T.-K.; Chen, C.-J.; Lee, D.-S.; Jong, T.-T.; Jiang, Y.-Z.; Mi, A.-Q. *Tetrahedron: Asymmetry*, **1996**, *7*, 57, and references cited therein.
5. For oxygen directing chiral dienes in cycloaddition please see: Tripathy, R.; Carroll, P. J.; Thornton, E. R. *J. Am. Chem. Soc.* **1991**, *113*, 7630, and references cited therein.
6. For nitrogen directing chiral dienes in cycloaddition please see: Murphy, J. P., and et. al. *Tetrahedron Letters*, **1995**, *36*, 9533, and references cited therein.
7. For sulfur directing chiral dienes in cycloaddition please see: (a) Gosselin, P.; Bonfand, E.; Hayes, P.; Retoux, R.; Maignan, C. *Tetrahedron: Asymmetry*, **1994**, *5*, 781. (b) Aversa, M. C.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron: Asymmetry*, **1994**, *5*, 805. (c) Arce, E.; Carmen Carreno, M.; Belen Cid, M.; Garcia Ruano, J. L. *J. Org. Chem.* **1994**, *59*, 3421, and references cited therein.
8. (a) Chou, T.-S.; Tso, H.-H. *Org. Prep. Proc. Int.*, **1989**, *21*, 257. (b) Chou, T.-S.; Chang, C.-Y.; Wu, M.-C.; Hung, S.-H.; Liu, H.-M.; Yeh, W.-Y. *J. Chem. Soc., Chem. Commun.*, **1992**, 1643.
9. Lee, D.-S.; Hung, S.-M.; Lai, M.-C.; Chu, H.-Y.; Yang, T.-K. *Org. Prep. Proc. Int.*, **1993**, *25*, 673.
10. Yang, T.-K.; et al. *J. Org. Chem.*, **1994**, *59*, 914.
11. Fujita, M.; Ishida, M.; Manako, K.; Sato, K.; Ogura, K. *Tetrahedron Letters*, **1993**, *34*, 645, and references cited therein.
12. The C-4 hydrogen atoms for **6*SR*** form cycloadducts were in the shielding cone of the imido carbonyl group, thus the chemical shifts of C-4 hydrogen for **6a*RS*** and **6b*RS*** were observed at δ 1.44 and 1.43 while the corresponding hydrogen in **6a*SR*** and **6b*SR*** resonated at δ 1.17 and 1.19, respectively.
13. ^{13}C NMR(75.4MHz, $CDCl_3$) **6a*RS*:** δ 11.22, 20.30, 20.90, 21.85, 24.96, 27.76, 32.80, 38.41, 38.69, 47.21, 48.76, 50.15, 71.45, 79.88, 125.62, 128.62, 129.00, 131.59, 134.63, 142.09, 177.61, 178.14. **6a*SR*:** δ 11.19, 20.19, 20.82, 21.64, 24.35, 28.36, 32.84, 38.79, 38.97, 47.08, 49.08, 50.04, 73.00, 79.47, 126.45, 128.57, 129.03, 131.70, 134.54, 142.83, 177.31, 177.92. **6b*RS*:** δ 11.49, 20.13, 20.51, 21.52, 24.18, 26.66, 28.50, 30.83, 32.47, 32.66, 38.72, 38.84, 46.81, 49.79, 50.93, 74.96, 84.01, 87.25, 126.48, 128.55, 129.01, 131.73, 133.10, 144.28, 177.20, 177.97. **6bSR:** δ 11.36, 20.19, 20.51, 21.61, 24.79, 26.58, 27.83, 32.32, 32.39, 38.49, 38.61, 46.76, 49.26, 50.96, 72.69, 83.91, 87.24, 125.89, 128.48, 128.90, 131.61, 133.48, 143.41, 177.58, 178.15.
14. Adams, H.; Neville Jones, D.; Aversa, M. C.; Bonaccorsi, P.; Giannetto, P. *Tetrahedron Letters*, **1993**, *34*, 6481.

(*Received in Japan* 8 *April* 1996; *revised* 7 *May* 1996; *accepted* 9 *May* 1996)