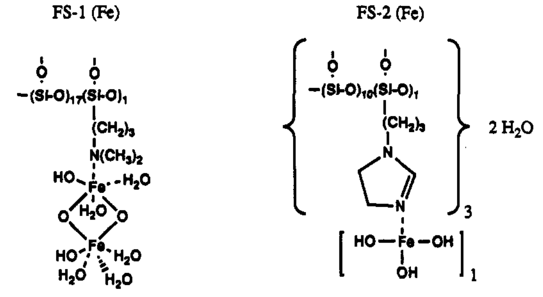
Scheme II. Plausible Structures for Fe Complexes FS-1 and FS-2



$Si_{18}O_{46}C_5H_{24}NFe_2$

calc. C: 4.13, H: 1.66, N: 0.97, Fe: 7.69
obs. C: 4.09, H: 1.72, N: 0.81, Fe: 7.60

$Si_{33}O_{75}C_{18}H_{48}N_6Fe$

calc. C: 9.37, H: 2.09, N: 3.64, Fe: 2.42
obs. C: 8.42, H: 2.77, N: 3.07, Fe: 2.32

oxidation of C–H bonds with dioxygen whereas those of FS-2 (Fe) would be inactive.

Cyclohexane oxidation was investigated with several complexes prepared from the functionalized silica gels.[8] It was observed that the compound which contains the dimethylamino group and two iron atoms [FS-1 (Fe)] is effective but that the compounds synthesized from other complexing ligands [FS-2 (Fe), FS-3 (Fe), and FS-4 (Fe)] were not active catalysts for oxidation (see Scheme I). The results of FS-1 are given in Table I.

Different metal complexes show different reactivities. The results are also shown in Table I. Runs 1, 2, and 8 are blanks. (Runs with various metals are 5, 6, 7, 8, 9, and 10.) The order of reactivity is Cu > Fe ≈ Mn ≈ Ni ≈ Co.

The stability constants for complex formation of metal ions with ethylenediamine diacetate as a ligand are known:[9] Fe^{2+} = 14.33; Co^{2+} = 16.21; Ni^{2+} = 18.52; Cu^{2+} = 18.79; and Fe^{3+} = 25.1. Making use of these constants and using for iron a mean value of Fe^{2+} and Fe^{3+}, Cu(II) might form the most stable complex with FS-1 compared with the other metals. When a stable complex reacts with dioxygen, a new reactive metal–oxygen complex is produced that is active as oxidizing catalyst.

The main product obtained from the oxidation of cyclohexane by the present method is cyclohexanol. In contrast, Barton[10] and co-workers observed cyclohexanone as the main product. This suggests that the mechanisms of the oxidations by these two reactions are different. We are investigating the mechanism by means of substituted cyclohexanes.

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(8) Representative oxidation procedure: To cyclohexane in a 100-mL round-bottom flask were added metal complexed FS, Zn powder, and acetic acid, and the suspension was stirred magnetically for a given time at room temperature under a static pressure of oxygen provided by a balloon. (A reviewer has suggested caution since a potentially explosive mixture could be generated. We experienced no problems, however, and add that the balloon was thin and the pressure was never greater than 1 atm. The system was always in the hood.) After the reaction, the contents of the flask were filtered and washed thoroughly with anhydrous ethyl ether. The combined organic extracts were distilled to a constant residual volume and this was analyzed by GC. Recovered cyclohexane was weighed. The only products were cyclohexanone and cyclohexanol. Quantitative GC analysis was carried out by the comparison of a standard cyclohexane–cyclohexanol–cyclohexanone calibration curve.

(9) Kayl, G. W. C.; Laby, T. H. *Tables of Physical and Chemical Constants and Some Mathematical Functions*; 14th ed.; Longman: 1973; p 225.

(10) Barton, D. H. R.; Boivin, J. B.; Gastiger, M.; Morzycki, J.; Hay-Motherwell, R. S.; Motherwell, W. B.; Ozbalik, N.; Schwartzentruber, K. M. *J. Chem. Soc., Perkin Trans. I* 1986, 947.

Powerful Dienophiles for Asymmetric Diels–Alder Reactions: α-(2-*exo*-Hydroxy-10-bornylsulfinyl)maleimides

Yoshitsugu Arai,[1a] Makoto Matsui,[1a] Toru Koizumi,*[,1a] and Motoo Shiro*[,1b]

Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani 2630, Toyama 930-01, Japan, and Shionogi Research Laboratories, Shionogi & Co., Ltd., Sagisu 5-12-4, Fukushima-ku, Osaka 553, Japan

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Summary: Enantiomerically pure *N*-substituted α-(2-*exo*-hydroxy-10-bornylsulfinyl)maleimides 1 have been synthesized diastereoselectively, and these dienophiles undergo Diels–Alder reactions readily with furan to give the corresponding cycloadducts with high diastereoselectivity.

The asymmetric Diels–Alder reactions using chiral dienes or dienophiles or chiral Lewis acid derivatives as promoters have received wide-spread attention during the past decade.[2] A number of applications of chiral dienophiles have been reported, including our studies in the area of chiral sulfoxides.[3-5] High asymmetric induction in the cycloadditions with reactive dienes such as cyclopentadiene has been achieved. In sharp contrast, few reports concerning asymmetric Diels–Alder reactions with furan have appeared because of its low reactivity.[4,5] Generally, the use of furan in a Diels–Alder reaction requires high-pressure conditions.[6] Although the high-pressure meth-

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(1) (a) Toyama Medical and Pharmaceutical University. (b) Shionogi Research Laboratories.

(2) For example, see; Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* 1984, *23*, 876. Taschner, M. J. In *Organic Synthesis: Theory and Applications*; Hudlicky, T., Ed.; JAI Press: Greenwich, CT, 1989; Vol. 1, pp 1–101.

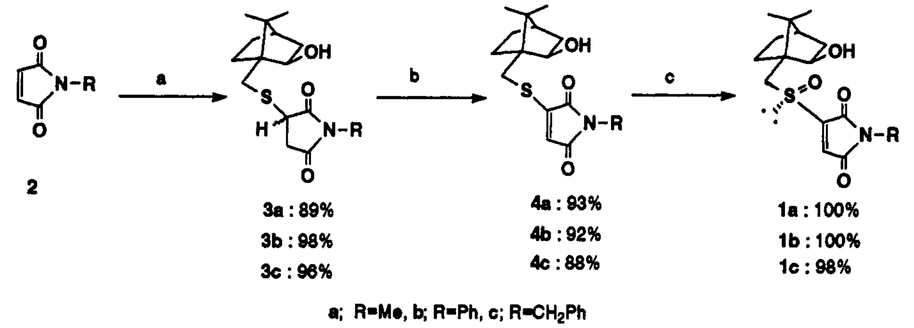
(3) Koizumi, T.; Hakamada, I.; Yoshii, E. *Tetrahedron Lett.* 1984, *25*, 87. Arai, Y.; Kuwayama, S.; Takeuchi, Y.; Koizumi, T. *Ibid.* 1985, *26*, 6205. Koizumi, T.; Arai, Y.; Takayama, H.; Kuriyama, K.; Shiro, M. *Ibid.* 1988, *29*, 3689. Arai, Y.; Takadoi, M.; Koizumi, T. *Chem. Pharm. Bull.* 1988, *36*, 4162.

(4) (a) Takayama, H.; Iyobe, A.; Koizumi, T. *J. Chem. Soc., Chem. Commun.* 1986, 771. Takayama, H.; Hayashi, K.; Takeuchi, Y.; Koizumi, T. *Heterocycles* 1986, *24*, 2137. Takayama, H.; Hayashi, K.; Koizumi, T. *Tetrahedron Lett.* 1986, *27*, 5509. Takayama, H.; Iyobe, A.; Koizumi, T. *Chem. Pharm. Bull.* 1987, *35*, 433.

(5) Mukaiyama, T.; Iwasawa, N. *Chem. Lett.* 1981, 29. Vieira, E.; Vogel, P. *Helv. Chim. Acta* 1983, *66*, 1865. Warm, A.; Vogel, P. *J. Org. Chem.* 1986, *51*, 5348. Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* 1990, 173. Reymond, J.-L.; Vogel, P. *J. Chem. Soc., Chem. Commun.* 1990, 1070.

0022-3263/91/1956-1983$02.50/0

Scheme I[a]



[a] Key: (a) 10-mercaptoisoborneol, Et_3N (cat.), PhH, rt, 6 h; (b) *N*-chlorosuccinimide, CCl_4, reflux, 6 h; (c) 3-chloroperoxybenzoic acid, CH_2Cl_2, -80 °C-rt, 3 h.

Table I. Diels-Alder Reactions of Sulfinylmaleimides 1 with Dienes[a]

entry	dienophile	diene	additive (1.5 equiv)	temp (°C)	time (h)	product (ratio)	isolated yield (%)
1	**1a**	cyclopentadiene	$ZnCl_2$	0	0.5	**5a**/**6a** (94:6)[b]	95
2	**1b**	cyclopentadiene	$ZnCl_2$	0	0.5	**5b**/**6b** (90:10)[b]	97
3	**1c**	cyclopentadiene	$ZnCl_2$	0	0.3	**5c**/**6c** (97:3)[c]	100
4	**1c**	cyclopentadiene	$ZnCl_2$	−78	0.5	**5c**/**6c** (97:3)[c]	97
5	**1c**	furan	$ZnCl_2$	−20	62	**7**/**8**/**9**/**10** (49:26:11:15)[c]	60
6	**1c**	furan	$ZnCl_2$	0	0.5	**7**/**8** (71:29)	66
7	**1c**	furan	$ZnCl_2$	0	60	**7**/**8** (68:32)	72
8	**1c**	furan	$ZnCl_2$	10	1	**7**/**8**/**9**/**10** (79:9:7:5)[c]	56
9	**1c**	furan	$ZnCl_2$	10	56	**7**/**8**/**9**/**10** (80:8:4:8)[c]	68
10	**1c**	furan	$ZnCl_2$	rt	20	**7**/**9** (55:45)	56
11	**1c**	furan	none	0	24	**7**/**8**/**9**/**10** (29:22:29:20)[c]	56
12	**1c**	furan	none	rt	5	**7**/**8**/**9**/**10** (22:32:24:22)[c]	54

[a] The reactions were carried out in dichloromethane as solvent and at 1-2 mmol (dienophile) scale. The major adducts **5** were separable from the minor products **6** by recrystallization. Diastereoisomers **7**-**9** were separable from each other by column chromatography; however, adduct **10** was inseparable from adduct **8** without the aid of HPLC. [b] Ratio was determined by ^1H NMR spectroscopy. [c] Ratio was determined by HPLC analysis.

odology is attractive for reactions that proceed inefficiently under conventional conditions, development of the Diels-Alder reaction under lower pressure conditions is more practical for large-scale preparation. Furthermore, the high-pressure procedure has the disadvantage that the cycloaddition products obtained under ultrahigh pressure (~1 GPa) often undergo cycloreversion at ambient or higher temperature. Recently, we demonstrated that (2-pyridylsulfinyl)acrylates react with furan to afford the Diels-Alder adducts with a high degree of diastereoselectivity.[4] Unfortunately, these reactions require long reaction times (~7 days) and suffer from unsatisfactory yields. This indicates a need for powerful chiral dienophiles that could effect a Diels-Alder reaction with dienes of low reactivity under conventional conditions. Herein, we show the first practically useful dienophile, chiral sulfinylmaleimides **1**, that react diastereoselectively with poor Diels-Alder dienes such as furan with short reaction times.

Sulfoxides **1** were easily prepared in three steps and excellent yields (Scheme I). Treatment of the maleimides **2** with 10-mercaptoisoborneol[7] gave the sulfides **3**.[8] Chlorination with *N*-chlorosuccinimide and subsequent elimination of hydrogen chloride afforded the maleimides **4**. Exposure of **4** to 3-chloroperoxybenzoic acid (*m*-CPBA) produced the sulfoxides **1**. The oxidation proceeded in a diastereoselective manner (de ~100%), and the configuration of the sulfinyl center could be tentatively assigned as *R*.[9] Although these sulfoxides are sensitive to acid, base, or silica gel, one crystallization of the crude oxidation product affords material satisfactory for use.

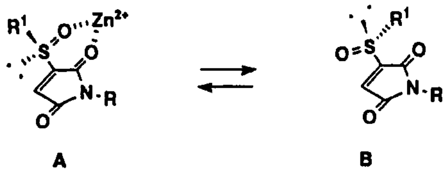


Figure 1.

The maleimides **1** were found to be quite reactive in cycloaddition reactions.[10] These results are summarized

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(6) Dauben, W.; Krabbenhoft, H. O. *J. Am. Chem. Soc.* **1976**, *98*, 1992. Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *Ibid.* **1980**, *102*, 6893. Kotsuki, H.; Nishizawa, H.; Ochi, M.; Matsuoka, K. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 496. Sera, A.; Ohara, M.; Kubo, T.; Itoh, K.; Yamada, H.; Mikata, Y.; Kaneko, C.; Katagiri, N. *J. Org. Chem.* **1988**, *53*, 5460. Katagiri, N.; Akatsuka, H.; Haneda, T.; Kaneko, C.; Sera, A. *Ibid.* **1988**, *53*, 5464. Katagiri, N.; Akatsuka, H.; Kaneko, C.; Sera, A. *Tetrahedron Lett.* **1988**, *29*, 5397. For recent successful examples of nonasymmetric Diels-Alder reactions with furan under conventional conditions, see: Ishar, M. P. S.; Wali, A.; Gandhi, R. P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2185. Grieco, P. A.; Nunes, J. J.; Gaul, M. D. *J. Am. Chem. Soc.* **1990**, *112*, 4595.

(7) Eliel, E. L.; Frazee, W. J. *J. Org. Chem.* **1979**, *44*, 3598.

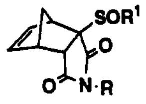
(8) Sulfides **3** were prepared according to a procedure similar to one reported previously; see: Kaydos, J. A.; Smith, D. L. *J. Org. Chem.* **1983**, *48*, 1096.

(9) Similar results in the oxidation of 10-(alkenylthio)isoborneols with *m*-CPBA have been observed; the secondary hydroxyl group determines the preferential attack of the oxidizing reagent in these reactions. Arai, Y.; Matsui, M.; Koizumi, T. *Synthesis* **1990**, 320; De Lucchi, O.; Lucchini, V.; Marchioro, C.; Valle, G.; Modena, G. *J. Org. Chem.* **1986**, *51*, 1457. Annunziata, R.; Cinquini, M.; Cozzi, F.; Farina, S.; Montanari, V. *Tetrahedron* **1987**, *43*, 1013. Eschler, B. M.; Haynes, R. K.; Kremmydas, S.; Ridley, D. D. *J. Chem. Soc., Chem. Commun.* **1988**, 137. **1a**: mp 152-153 °C; $[\alpha]^{23}_D$ −12° (*c* 1.0, $CHCl_3$). **1b**: mp 129-131 °C; $[\alpha]^{24}_D$ +89.2° (*c* 0.97, $CHCl_3$). **1c**: mp 58-60 °C; $[\alpha]^{26}_D$ +45.8° (*c* 1.0, $CHCl_3$). From the X-ray analyses (see ref 13), the absolute configuration of the sulfinyl center of the dienophile **1c** was confirmed to be *R*.

in Table I, indicating some notable features. Under chelation-controlled conditions, the Diels–Alder reaction with cyclopentadiene proceeded with high diastereofacial selectivity to give the corresponding adducts (entries 1–4). It should be noted that the product ratios derived from furan were dependent entirely on the reaction temperature (entries 5–10). At 0 °C (entries 6 and 7), the diastereofacial selectivities for endo and exo additions are ~100%, while the endo/exo selectivities are low. In contrast, for reactions at 10 °C (entries 8 and 9), the endo/exo selectivities are remarkably high. The reaction conducted at room temperature afforded the *exo*-sulfinyl adducts exclusively (entry 10).

This observation indicates that the kinetically favored initial *exo*-sulfinyl products undergo isomerization to thermodynamically more stable *endo*-sulfinyl adducts via dissociation and recombination. Under chelation-controlled conditions, sulfoxides 1 would exist predominantly in conformation A where the zinc metal could coordinate with one of the imido carbonyl groups and the sulfinyl oxygen, resulting in preferential attack of a diene on the less hindered lone-pair side (Figure 1). In the absence of a Lewis acid, 1 would exist in both A and the conformation B due to the dipole–dipole repulsion.

The stereochemistry of the *exo*-sulfinyl adducts 5 and 6 was confirmed by transformation into the known *endo*-maleimide adducts 11[11] by samarium-induced reduction,[12] which also allowed efficient recovery of the chiral auxiliary, 10-mercaptoisoborneol. The absolute stereochemistry of **5c** and 7 was established by X-ray crystallography.[13] The exo orientation of the sulfinyl group in 8 and 10 was determined by the coupling constant (J = 5 Hz) between the H-3 and H-4 protons, whereas both H-3 protons in 7 and 9 appear as singlets. The absolute stereostructures of 5–10 should be tentatively assigned on the basis of the proposed mechanism we reported previously,[3] except for **5c** and 7. The utility of the adducts is exemplified by the following transformation into a ω-carbinol lactam, which is known to be a useful precursor for synthesis of nitrogen-containing natural products based on the *N*-acyliminocyclization strategy.[14] Adduct **5c** was thus transformed into lactam 12 by selective reduction with sodium borohydride in 94% yield. The regioselectivity in the reduction of the imido carbonyl in a rigid bridged system such as **5c** can be explained by steric factors[15] in contrast to bicyclic anhydrides and succinimides.[16] Treatment of 12 with samarium diiodide in the presence of hexamethylphosphoric triamide (HMPA)[17] gave the optically active ω-carbinol lactam 13 in 60% yield.



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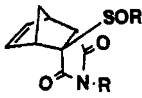

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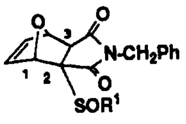

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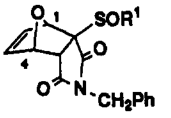

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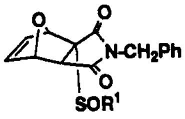

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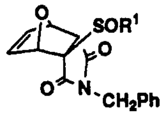

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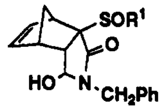

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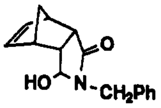

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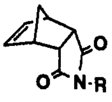

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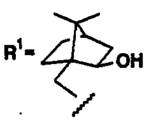

a; R=Me, b; R=Ph, c; R=CH₂Ph

As described previously, sulfinylmaleimides 1 are easily prepared as single diastereoisomers and the chelation-controlled Diels–Alder reaction proceeded with high diastereoselectivity. Application of the adducts to natural product synthesis is in progress.

Acknowledgment. This work was supported by the Research Foundation for Pharmaceutical Sciences, the TERUMO Life Science Foundation, and the Yamada Science Foundation, to which we are grateful.

Supplementary Material Available: Procedures for the preparation of 1, physical and combustion data for **1a–c**, **3a–c**, **4a–c**, 7, 12, and 13, and X-ray crystallographic data for **5c** and 7 (17 pages). Ordering information is given on any current masthead page.

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(10) The dienophiles react with anthracene and cyclohexa-1,3-diene in the presence of $ZnCl_2$ smoothly and diastereoselectively to afford single adducts.

(11) Morgan, M. S.; Tipson, R. S.; Lowy, A.; Baldwin, W. E. *J. Am. Chem. Soc.* **1944**, *66*, 404. Culberson, C. F.; Wilder, P., Jr. *J. Org. Chem.* **1960**, *25*, 1358.

(12) Molander, G. A.; Hahn, G. *J. Org. Chem.* **1986**, *51*, 1135. Arai, Y.; Matsui, M.; Koizumi, T. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1233.

(13) Crystal data are as follows: **5c** $C_{26}H_{31}NO_4S$, FW 453.6, monoclinic, space group $P2_1$, a = 14.917 (2) Å, b = 7.129 (1) Å, c = 11.137 (2) Å, V = 1172.2 (3) Å^3, Z = 2, independent reflections 1404, final residual value R = 0.042; 7 $C_{25}H_{29}NO_5S$, FW 455.6, monoclinic, space group $P2_1$, a = 9.742 (1) Å, b = 16.703 (3) Å, c = 7.041 (2) Å, V = 1144.7 (4) Å^3, Z = 2, independent reflections 975, final residual value R = 0.051.

(14) For example, see: Wijnberg, B. P.; Speckamp, W. N.; Oostveen, A. R. C. *Tetrahedron* **1982**, *38*, 209. Speckamp, W. N.; Hiemstra, H. *Ibid.* **1985**, *41*, 4367.

(15) Kayser, M. M.; Wipff, G. *Can. J. Chem.* **1982**, *60*, 1192. Kayser, M. M.; Salvador, J.; Morand, P.; Krishnamurty, H. G. *Ibid.* **1982**, *60*, 1199.

(16) Vijn, R. J.; Hiemstra, H.; Kok, J. J.; Knotter, M.; Speckamp, W. N. *Tetrahedron* **1987**, *43*, 5019.

(17) Without HMPA, the reaction did not proceed. It has been well-established that the addition of HMPA accelerates reductions with samarium diiodide; see: Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.