

(1*R*,3*R*)-2-Methylene-1,3-dithiolane 1,3-Dioxide: A Highly Reactive and Highly Selective Chiral Ketene Equivalent

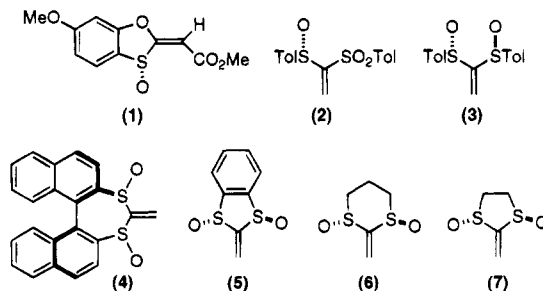
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Ketene equivalents have found widespread use as partners in Diels–Alder reactions for the construction of cyclic, fused, and bridged unsaturated ketones.¹ Furthermore, the versatile functionality contained in the products provides useful handles for further manipulation. The current interest in the synthesis of enantiomerically pure compounds has fueled activity in the design of chiral ketene equivalents,^{2–4} and those based on alkenyl sulfoxides have proved to be an attractive area of study owing to the possibility of asymmetric induction.^{5,6} However, ketene equivalents based on simple vinyl⁷ sulfoxides are poor dienophiles and show low levels of diastereocontrol, except when activated as sulfonium salts by alkylation of the sulfinyl oxygen.⁸ Vinyl sulfoxide **1** possessing a second electron-withdrawing group at the β -position shows high selectivity in Diels–Alder reactions with cyclopentadiene under Lewis acid catalysis.⁹ However, additional steps are required in the subsequent removal of this group for **1** to act as a true ketene equivalent.⁹ Vinyl sulfoxide **2** possessing a sulfone group at the α -position also shows good diastereoselectivity under Lewis acid catalysis and has been employed as a ketene equivalent with cyclopentadiene.¹⁰ Vinyl bis-sulfoxides **3**¹¹ and **4**¹² are also more reactive than simple vinyl sulfoxides in Diels–Alder reactions, but again only show modest levels of diastereocontrol. We have shown¹³ that the C_2 -symmetric cyclic alkenyl sulfoxides (\pm)-**5** and (\pm)-**6** show increased selectivity over those previously reported and now report that the simpler analogue, *trans*-2-methylene-1,3-dithiolane 1,3-dioxide, **7**, shows levels of reactivity and diastereoselectivity superior to the cyclic

sulfoxides (\pm)-**5** and (\pm)-**6** and better than the other ketene equivalents currently available.



The preparation of **7** in enantiomerically pure form required only four steps and is shown in Scheme 1. Transthioketalization of the commercially available acetal **8** under acid catalysis¹⁴ gave dithiolane **9** in high yield. Asymmetric oxidation of dithiolane **9** using the Modena protocol¹⁵ gave the (*R,R*)-bis-sulfoxide¹⁶ **10** in good yield and as essentially a single enantiomer *even before recrystallization*.¹⁷ In related studies, we have previously found very high levels of enantiomeric excess in the asymmetric bis-oxidation of 2-substituted 1,3-dithianes which we believe is a consequence of carrying out two asymmetric transformations in the same pot.^{15d} Finally, elimination of **10** to give the required alkene **7** was achieved in two steps *via* formation of the amine **11** and subsequent treatment with methyl iodide and base.

The results of Diels–Alder reactions between ($-$)-**7** and a range of dienes are summarized in Table 1. Reaction with cyclopentadiene occurred readily in propionitrile¹⁸ at room temperature giving a 90:10 ratio of **12a:12b**, while at -78 °C, using $\text{BF}_3 \cdot \text{OEt}_2$ catalysis, the *adduct 12a was obtained as a single diastereoisomer* (entry 1).¹⁹ Diels–Alder reactions with acyclic dienes occurred conveniently at room temperature giving *single diastereomeric adducts* and in excellent yield without the necessity

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(16) Assignment of the absolute stereochemistry of **10** was initially based on correlation with the literature (ref 15b) and confirmed by single crystal X-ray analysis on the Diels–Alder adduct **14a** and subsequent synthesis of the known norbornenone **17**.

(17) Chiral HPLC analysis was carried out on a Chiralpak AD column (25 \times 4.6 mm i.d.) eluting with 87% petroleum ether/12% isopropyl alcohol/1% diethylamine at 2 mL/min and using a UV detector at 240 nm. (*R,R*)-**10** had a retention time of 16.7 min while (*S,S*)-**10** had a retention time of 15.8 min. We were unable to detect the minor (*S,S*) enantiomer before and after recrystallization.

(18) Propionitrile gave higher selectivity compared with other solvents.

(19) Lewis acids have been shown to cause racemization of sulfoxides: Mikolajczyk, M.; Drabowicz, J. *Top. Stereochem.* **1982**, 13, 411. However, no racemization occurred with either dienophile **7** or Diels–Alder adducts **12–15**. We have previously found *trans*-1,3-dithiane 1,3-dioxide to be reluctant to undergo equilibration of the sulfinyl groups: Aggarwal, V. K.; Davies, I. W.; Franklin, R.; Maddock, J.; Mahon, M. F.; Molloy, K. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2363.

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[⊥] (1) For a review see: Ranganathan, S.; Ranganathan, D.; Mehrotra, A. K. *Synthesis*, **1977**, 289.

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(4) For an alternative catalytic approach see: (a) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, 113, 8966. (b) Corey, E. J.; Loh, T.-P. *Tetrahedron Lett.* **1993**, 34, 3979.

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(7) (a) Maignan, C.; Raphael, R. A. *Tetrahedron* **1983**, 39, 3245. (b) Katagiri, N.; Ise, S.; Watanabe, N.; Kaneko, C. *Chem. Pharm. Bull.* **1990**, 38, 3242.

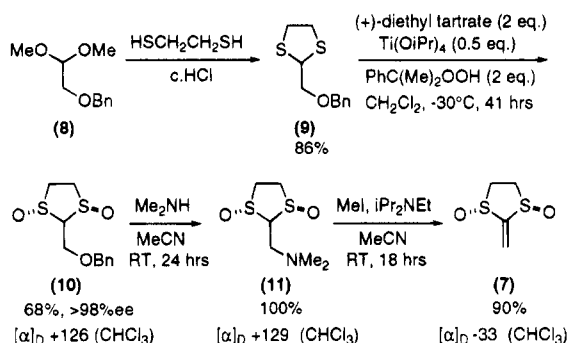
(8) Ronan, B.; Kagan, H. B. *Tetrahedron Asymmetry* **1991**, 2, 75.

Table 1. Diels-Alder Reactions between Dienophile (–)-7 and a Range of Dienes

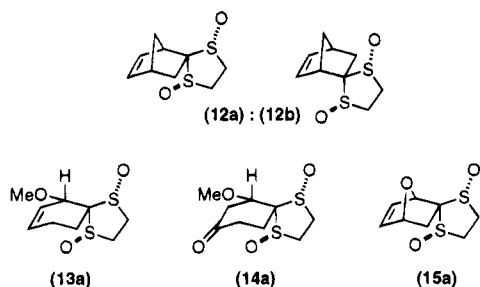
entry	diene ^a	Lewis acid	T (°C)	time	Diels-Alder adducts ^b	ratio of adducts (a:b) ^c	isolated yield (%)
1	cyclopentadiene	BF ₃ ·OEt ₂	–78	20 min	12a:12b	>97:3	74
2	1-methoxybutadiene	–	rt	18 h	13a:13b	>97:3	83
3	1-methoxy-3-trimethylsilyloxybutadiene	–	rt	2 h	14a:14b	>97:3	90
4	furan	SnCl ₄	–78	30 min	15a:15b	>97:3	65

^a All reactions were conducted in EtCN. ^b The relative stereochemistry of all major adducts (**12a**–**15a**) have been determined by X-ray crystallography. ^c Determined by ¹H NMR integration of crude reaction mixtures.

Scheme 1



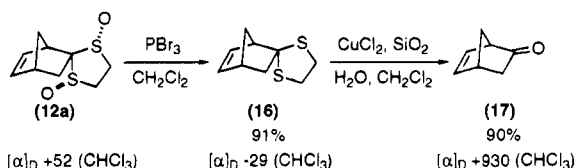
of using Lewis acids (entries 2 and 3). Surprisingly, reaction with the much less reactive diene, furan, also occurred readily, this time under SnCl₄ catalysis, giving the adduct **15a** again as a *single diastereoisomer* (entry 4).



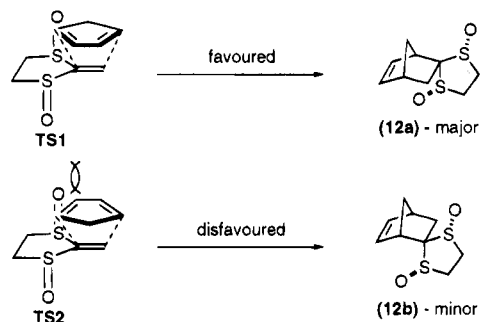
The stereochemical outcome of the Diels-Alder reactions may be rationalized by considering the two possible transition states **TS1** and **TS2**. **TS2** suffers from non-bonded steric interactions between the vinyl substituent on the diene and the sulfinyl oxygen, whereas in **TS1** the vinyl substituent on the diene only interacts with a lone pair.²⁰ Electronic factors may also be important in determining the stereochemical outcome of the reaction. Since the interactions of lone pairs on oxygen with π systems are repulsive²¹ this phenomenon will further destabilize **TS2** relative to **TS1**.

(20) For other examples of selective Diels-Alder reactions resulting from the difference in size between a sulfinyl oxygen and a lone pair see: (a) Waldner, A. *Tetrahedron Lett.* **1989**, *30*, 3061. (b) Reference 9. (c) Fisher, M. J.; Hehre, W. J.; Kahn, S. D.; Overman, L. E. *J. Am. Chem. Soc.* **1988**, *110*, 4625. For a contrary example of a cycloaddition occurring on the face bearing a sulfinyl oxygen in preference to the face bearing a sulfinyl lone pair see: (d) Naperstkw, A. M.; Macaulay, J. B.; Newlands, M. J.; Fallis, A. G. *Tetrahedron Lett.* **1989**, *30*, 5077. (21) McCarrick, M. A.; Wu, Y.-D.; Houk, K. N. *J. Am. Chem. Soc.* **1992**, *114*, 1499 and references cited therein.

Scheme 2



The bis-sulfoxide moiety can be readily deprotected using a two-step sequence which is demonstrated for the cyclopentadiene adduct **12a**, Scheme 2. Sulfoxide reduc-



tion followed by hydrolysis of the dithiolane²² using standard conditions gave enantiomerically pure norbornenone **17**.²³

In summary, we have developed a new chiral ketene equivalent which (a) can be readily obtained in four steps, (b) shows the highest levels of selectivity yet achieved for a wide range of different dienes, and (c) can be readily deprotected to afford enantiomerically pure cyclic, fused, or bridged unsaturated ketones.

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Supporting Information Available: Experimental procedures and spectral data for compounds **7** and **9**–**17** (5 pages).

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(23) Chiral GC analysis of (\pm)-**17** was carried out on a Chiraldex G-TA column (30 m \times 0.25 mm i.d.), using hydrogen as the carrier gas at a flow rate of 1.7 mL/min, 55 °C isothermal, flame ionization detection. (+)-**17** had a retention time of 13.9 min while (–)-**17** had a retention time of 13.5 min. The enantiomeric excess of the product obtained was determined to be >98%.