Chiral, Bisfunctionalization of Substrates: A Powerful Strategy for the Asymmetric Synthesis of C_2 Symmetric Compounds and Its Application to the Synthesis of Enantiomerically Pure *trans*-1,3-Dithiane 1,3-Dioxide†

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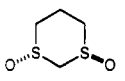
Summary: We have found that the chiral, bisfunctionalization of substrates is a powerful strategy for the preparation of C_2 symmetric compounds with very high enantiomeric excess, and by applying this strategy with the Modena method for the asymmetric oxidation of sulfides we have prepared (1*R*,3*R*)-1,3-dithiane 1,3-dioxide (1) in enantiomerically pure form.

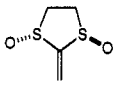
C_2 Symmetric reagents are finding increasing attention in asymmetric synthesis as a result of the generally high selectivities that are obtained with them.[1] This symmetry feature in one of the substrates reduces the number of competing diastereomeric transition states of a chemical reaction by half and thereby increases the diastereoselectivity of the process.[2]

A powerful strategy for the synthesis of C_2 symmetric reagents that require the introduction of two asymmetric centers from an external source (rather than C_2 symmetric reagents derived from natural compounds with C_2 symmetry, e.g., tartaric acid) is to carry out both asymmetric processes simultaneously. It is important that such asymmetric processes occur with good reagent control to favor formation of optically active products;[3] otherwise, under substrate-controlled processes meso compounds predominate.[4] This bisfunctionalization strategy is not commonly used but lends itself not only to greater efficiency but also it can lead to products with very high enantioselectivity.[5,6]

We have investigated the chemistry of the C_2 symmetric reagents *trans*-1,3-dithiane 1,3-dioxide (1) and 2-methylene-*trans*-1,3-dithiolane 1,3-dioxide (2) and found



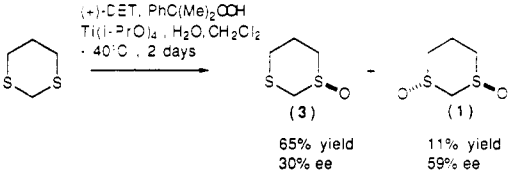
(1)



(2)

that the former reagent undergoes highly diastereoselective reactions with aromatic aldehydes[7] while the latter reagent undergoes highly diastereoselective cycloadditions.[8] These reagents act as potential chiral acyl anion equivalents and chiral ketene equivalents, respectively. In order to realize this potential we need to be able to prepare these auxiliaries in enantiomerically pure form and hydrolyze the auxiliary at the end. In this paper we demonstrate a powerful and general strategy for the synthesis of C_2 symmetric compounds and its application to a highly enantioselective and facile synthesis of *trans*-1,3-dithiane 1,3-dioxide (1).

We chose to examine the asymmetric bisoxidation of 1,3-dithiane to the dioxide 1 and, of the different oxidation methods available,[9-11] chose the Kagan protocol[9] due to its wide usage and ready availability of reagents. However, after subjecting 1,3-dithiane to the Kagan oxidation for 2 days at −40 °C we obtained the monoxide 3 with low enantioselectivity together with a small amount of the dioxide 1 but again with only moderate enantioselectivity (see later for method of ee determination). It is interesting to note that the calculated enantiomeric excess of the dioxide, assuming no kinetic resolution and no double stereodifferentiation, is in close agreement to the measured enantiomeric excess of the dioxide.[12]



To obtain very high levels of enantioselectivity in the bisoxidation process it is necessary for the initial oxidation to occur with relatively high enantioselectivity, and toward this end Kagan has reported that high levels of enantioselectivity in the oxidation of 1,3-dithiane derivatives can be obtained if they possess certain groups in the 2-position.[13] We therefore sought a temporary group for

† This paper is dedicated to Professor Stork on the occasion of his 70th birthday.

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(1) For a recent review on C_2 symmetry see: Whitesell, J. K. *Chem. Rev.* **1989**, *89*, 1581.

(2) Najdi, S.; Kurth, M. J. *Tetrahedron Lett.* **1990**, *31*, 3279.

(3) For a general discussion see: Schreiber, S. L. *Chem. Scripta* **1987**, *27*, 563.

(4) For an example of the use of this strategy in synthesis see: Still, W. C.; Barish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.

(5) This is demonstrated as follows. In theory, if a reaction gives an *x*:*y* ratio of enantiomers for a monofunctionalized compound then the ratio of enantiomers for the bisfunctionalized compound is x^2:y^2 assuming that no kinetic resolution and no double stereodifferentiation occurs. For example, if the first asymmetric process gives a 9:1 ratio of enantiomers (*R*:*S*) and the reaction occurs a second time on this mixture one should obtain an 81:9:9:1 ratio of products (*RR*:*RS*:*SR*:*SS*), again assuming that no kinetic resolution had occurred and that the second asymmetric process also occurred with the same 9:1 selectivity. Thus, bisfunctionalization has raised the ee from 80% (for the monofunctional compound) to 97.5%.

(6) For literature examples see: (a) Hoye, T. R.; Suhadolink, J. C. *Tetrahedron*, **1986**, *42*, 2855. (b) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.*, **1988**, *110*, 629. (c) Wang, Z.; Deschenes, D. *J. Am. Chem. Soc.* **1992**, *114*, 1090. (d) Soai, K.; Hori, H.; Kawahara, M. *J. Chem. Soc. Chem. Commun.* **1992**, 106.

(7) Aggarwal, V. K.; Franklin, R. J.; Rice, M. J. *Tetrahedron Lett.* **1991**, *32*, 7743.

(8) Aggarwal, V. K.; Lightowler, M.; Lindell, S. D. Manuscript submitted to *Tetrahedron Lett.*

(9) (a) Pitchen, P.; Dunach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188. (b) Zhao, S. H.; Samuel, O.; Kagan, H. B. *Tetrahedron* **1987**, *43*, 5135. (c) For a review see: Kagan, H. B.; Rebiere, F. *Synlett* **1990**, 643.

(10) Di Furia, F.; Modena, G.; Seraglia, R. *Synthesis 1984*, 325.

(11) (a) Davis, F. A.; Thimma Reddy, R.; Weismiller, M. C. *J. Am. Chem. Soc.*, **1989**, *111*, 5964. (b) Davis, F. A.; Thimma Reddy, R.; Han, W.; Carroll, P. J. *J. Am. Chem. Soc.*, **1992**, *114*, 1428. (c) A comparison of the Davis, Kagan, and enzymatic oxidation of vinyl sulfides has recently been carried out: Rossi, C.; Fauve, A.; Madesclaire, M.; Roche, D.; Davis, F. A.; Thimma Reddy, R. *Tetrahedron Asymm.* **1992**, 629.

(12) Using the above formula (see ref 5), a 65:35 ratio of enantiomers of the monoxide (30% ee) corresponds to a calculated 77.5:22.5 ratio of enantiomers of the dioxide (55 % ee). The observed enantiomeric excess of the dioxide is 59%.

(13) (a) Samuel, O.; Ronan, B.; Kaga, H. B. *J. Organomet. Chem.* **1989**, *370*, 43. During the course of this work Page also reported that high levels of enantioselectivity were obtained during Kagan oxidation of 2-acyl-1,3-dithianes. (b) Page, P. C. B.; Namwindwa, E. S.; Klair, S. S.; Westwood, D. *Synlett* **1990**, 457. (c) Page, P. C. B.; Namwindwa, E. S. *Synlett* **1991**, 80.

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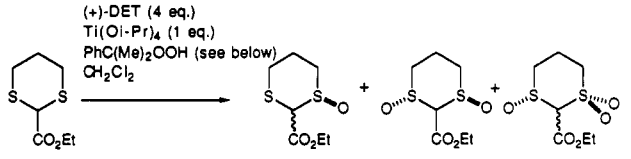
the 2-position that would deliver good enantioselectivity in the oxidation process and one that could be readily removed at the end. The carbethoxy group was chosen as the temporary group since the starting material 4 is commercially available and since it was expected that base-catalyzed hydrolysis and decarboxylation of the dioxide ester 6 would give the target compound.

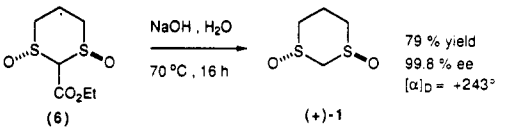


CHP				
2 eq.		60% (85% ee)	38% (>97%ee)	0%
4 eq.	at -35°C, 2 days	28% (82% ee)	68% (>97%ee)	0%
6 eq.		0%	20% (>97%ee)	38%
4 eq	at -20°C, 1 day	12% (84% ee)	80% (>97%ee)	4%

In an extensive study we found the Modena modification[10] superior to the Kagan oxidation for substrate 4.[14] Modena oxidation of 4 at −35 °C using 2 equiv of oxidant gave a mixture of cis and trans monoxides 5 with good enantiomeric excess together with a small amount of diastereomerically pure trans dioxide 6.[15] The dioxide appeared to be a single enantiomer by integration of the ^{1}H NMR spectrum in the presence of Eu(hfc)$_3$ shift reagent. Increasing the stoichiometry of the oxidant resulted in an increase in the yield of the dioxide formed, although a large excess of peroxide resulted in some overoxidation to the sulfoxide–sulfone 7. Optimum conditions required 4 equiv of the oxidant for 1 day[16] at −20 °C, and the dioxide obtained appeared to be a single enantiomer by NMR.[17] In contrast to Kagan oxidation[13a] there is little variation in the level of enantioselectivity with temperature under the Modena conditions.

The absolute stereochemistry of 6 has been assigned as 1*R*,3*R* in accordance with literature precedent.[18]

Finally, hydrolysis and decarboxylation was readily achieved by heating 6 in aqueous base at 70 °C. Following workup and isolation, enantiomerically pure 1,3 dithiane 1,3-dioxide [(+)-1] was obtained. Using the Pirkle shift reagent, TFAE[19] (TFAE gave superior results compared to Eu(hfc)$_3$) we determined that the enantiomeric excess[20] of 1 was >99.5% and that no epimerization of the sulfoxide chiral centers had taken place during the decarboxylation of the ester.



In conclusion, the strategy of chiral, bisfunctionalization of substrates has been applied to the asymmetric oxidation of 4 using the Modena protocol. This gives the corresponding dioxide in high yield and in exceptionally high enantiomeric excess. Hydrolysis and decarboxylation gives the title compound in enantiomerically pure form.

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Supplementary Material Available: Experimental procedures and compound data (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(14) Modena oxidation gave higher yields of the dioxide compared to the Kagan protocol. Under Kagan conditions it was not possible to make the reaction go to completion even by increasing the stoichiometry of the oxidant; the main product obtained was the monoxide. We believe that the Modena system is a significantly stronger oxidant than the Kagan system.

(15) Page (ref 13b) also observed the formation of small quantities of the trans dioxides of 2-substituted 1,3-dithianes under the Kagan oxidation conditions.

(16) Leaving the reaction for longer periods of time (>1 day at −20 °C or >2 days at −35 °C) did not increase the yield of the dioxide 6 but resulted in partial overoxidation to the sulfoxide–sulfone 7.

(17) An initial ee of 85% for the monoxide would give rise to dioxide with a calculated ee of 98.7%. Since little kinetic resolution is occurring under the reaction conditions a small quantity of the meso cis dioxide must also be produced. However, we have been unable to isolate this product and can only presume that the cis isomer precipitates out and is lost upon filtration of the titanium residues. In comparison, the cis diastereoisomer of 1 is very much more polar and crystallizes more readily than 1 itself. Alternatively, it is possible that the cis diastereoisomer of 6 is oxidized to the sulfone–sulfoxide 7 more readily than the trans isomer. We have observed that the cis diastereoisomer of 1 is oxidized ~3× more rapidly than *trans*-1 by $NaIO_4$.

(18) Kagan has reported the absolute configuration of 5 (see ref 13a). From this we have assigned the absolute configuration of 6.

(19) TFAE = (trifluoroanthracenyl)ethanol. Pirkle, W. H.; Hoover, D. J. *Top. Sterochem.* **1982**, *13*, 263.

(20) Measurement of the optical purity of the dioxide was initially problematic. While the enantiomeric excess of the dioxide ester 6 was determined using the chiral shift reagent, Eu(hfc)$_3$, in $CDCl_3$ this was not possible for dithiane dioxide 1 due to its insolubility. Unfortunately, very polar solvents that are required to solubilize 1 are not normally compatible with chiral shift reagents due to the overwhelming chelation of the donor aprotic solvent to the metal. However, we are gratified to find that not only did D-3 acetonitrile solubilize 1 but appreciable splitting of the C-2 protons for the individual enantiomers was observed with the experiments with TFAE. It was also possible, by carrying out doping experiments with a small amount of the racemate (2%), to detect the other enantiomer at very low levels of concentration (0.5%).