JOC*Note*

Highly Enantioselective Oxidations of Ketene Dithioacetals Leading to Trans Bis-sulfoxides

Varinder K. Aggarwal,*,† Rebecca M. Steele,† Ritmaleni,† Juliet K. Barrell,† and Ian Grayson‡

School of Chemistry, University of Bristol, Cantock's Close, Bristol BS8 1TS, U.K., and Degussa Fine Chemicals, Seal Sands, Middlesbrough TS2 1UB, U.K.

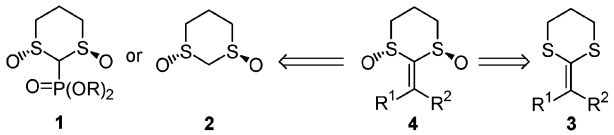
v.aggarwal@bristol.ac.uk

Received January 9, 2003

Abstract: Ketene dithioacetals undergo a Sharpless-type asymmetric oxidation using (+)-DET, $Ti(O^iPr)_4$, and cumene hydroperoxide to give the trans bis-sulfoxides **4a**−**f** with essentially complete control of enantioselectivity and diastereoselectivity. The high enantioselectivity is a consequence of carrying out two asymmetric processes on the same substrate. However, this should lead to the formation of a small amount of the meso isomer but none was isolated. From monitoring the enantioselectivity of the monoxide over time, it was concluded that small amounts of the meso isomer must be formed. The inability to isolate this compound could be because it acted as a ligand on titanium and remained tightly bound even upon workup.

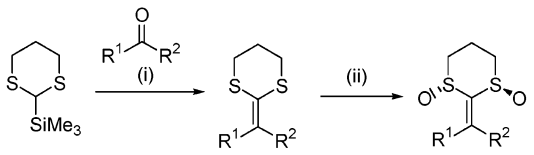
Ketene dithioacetals are useful intermediates in organic synthesis as they are able to participate in a variety of [3 + 2] and [4 + 2] cycloaddition reactions.[1] The corresponding mono- or bis-sulfoxides are potentially capable of performing such reactions with good to excellent diastereocontrol,[2] thus leading to products with high enantiomeric excess after deprotection. Indeed, we have shown that chiral ketene dithioacetal bis-sulfoxides undergo inter-[3] and intramolecular[4] [3 + 2] nitrone cycloadditions and [4 + 2] Diels−Alder[5] reactions with essentially complete diastereocontrol. In addition, the ketene dithioacetal bis-sulfoxides also undergo highly diastereoselective nucleophilic epoxidation reactions, and the intermediate epoxides react stereospecifically with amines to generate enantiopure α-aminoamides.[6] In the above cases, the ketene dithioacetal bis-sulfoxides were prepared by either a Wittig−Horner reaction with phosphonate **1** or an aldol-type reaction with bis-sulfoxide **2** (Scheme 1).

SCHEME 1. Possible Routes to Ketene Dithioacetal Bis-sulfoxides



1 **2** **4** **3**

SCHEME 2. Route to Ketene Dithioacetal Bis-sulfoxides[a]



5 **3a-f** **4a-f**

4a:R^1=H, R^2=$(CH_2)_3CH_3$
4b:R^1=H, R^2=C_6H_{11}
4c:R^1/R^2=cyclo-$(CH_2)_5$
4d:R^1=H, R^2=Ph
4e:R^1=H, R^2=*p*-$MeOC_6H_4$
4f:R^1=Me, R^2=Ph

[a] Reagents and conditions: (i) *n*-BuLi, THF, −78 °C to rt; (ii) $Ti(O^iPr)_4$ (0.5 equiv), (+)-DET (2 equiv), $PhC(Me)_2OOH$ (4 equiv), CH_2Cl_2, −40 to −20 °C.

Although we have developed efficient and highly enantioselective routes to **1** and **2**, we questioned whether the ketene dithioacetal bis-sulfoxides could be prepared more directly and in higher yield by oxidation of ketene dithioacetals **3** (Scheme 2). A further motivation for this strategy came from the sensitivity of dithiane dioxides **1** and the precursor of **2** to acid/Lewis acid (present in the oxidation process), which resulted in a facile Pummerer reaction leading to partial decomposition and thus reduced yields. Such processes were clearly not possible with ketene dithioacetals **3**. Although there were numerous examples of asymmetric oxidation of 1,3-dithianes with substituents in the 2-position, to give mono-sulfoxides with good ee[7] and bis-sulfoxides with essentially complete selectivity,[5b,c,6,8] there were no examples of the asymmetric oxidation of ketene dithioacetals. We therefore embarked on this study.

A range of ketene dithioacetals was prepared by Peterson olefination of dithiane **5**[9] with aldehydes and ketones. These substrates were then subjected to our previously developed conditions for oxidation of 1,3-

† Degussa Fine Chemicals.
‡ University of Bristol.

(1) For reviews, see: (a) Aggarwal, V. K.; Ali, A.; Coogan, M. P. *Tetrahedron* **1999**, *55*, 293−312. (b) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423−5506. (c) Kolb, M. *Synthesis* **1990**, 171−190.

(2) (a) Ruano, J. L. G.; de la Plata, B. C. *Top. Curr. Chem.* **1999**, *204*, 1−126. (b) Ruano, J. L. G.; Carretero, J. C.; Carreno, M. C.; Cabrejas, L. M. M.; Urbano, A. *Pure Appl. Chem.* **1996**, *68*, 925−930. (c) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760. (d) Lopez, R.; Carretero, J. C. *Tetrahedron*: *Asymmetry* **1991**, *2*, 91−92.

(3) Aggarwal, V. K.; Grainger, R. S.; Adams, H.; Spargo, P. L. *J. Org. Chem.* **1998**, *63*, 3481−3485.

(4) Aggarwal, V. K.; Roseblade, S. J.; Barrell, J. K.; Alexander, R. *Org. Lett.* **2002**, *4*, 1227−1229.

(5) (a) Aggarwal, V. K.; Lightowler, M.; Lindell, S. D. *Synlett* **1992**, 730−731. (b) Aggarwal, V. K.; Drabowicz, J.; Grainger, R. S.; Gültekin, Z.; Lightowler, M.; Spargo, P. L. *J. Org. Chem.* **1995**, *60*, 4962−4963. (c) Aggarwal, V. K.; Gültekin, Z.; Grainger, R. S.; Adams, H.; Spargo, P. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2771−2781.

(6) Aggarwal, V. K.; Barrell, J. K.; Worrall, J. M.; Alexander, R. *J. Org. Chem.* **1998**, *63*, 7128−7129.

(7) (a) Page, P. C. B.; McKenzie, M. J.; Buckle, D. R. *Tetrahedron* **1998**, *54*, 14581−14596. (b) Samuel, O.; Ronan, B.; Kagan, H. B. *J. Organomet. Chem.* **1989**, *370*, 43−50.

(8) (a) Aggarwal, V. K.; Esquivel-Zamora, B. N.; Evans, G. R.; Jones, E. *J. Org. Chem.* **1998**, *63*, 7306−7310. (b) Aggarwal, V. K.; Evans, G.; Moya, E.; Dowden, J. *J. Org. Chem.* **1992**, *57*, 6390−6391.

(9) (a) Seebach, D.; Kolb, M.; Gröbel, B.-T. *Chem. Ber.* **1973**, *106*, 2277−2290. (b) Seebach, D.; Kolb, M.; Gröbel, B.-T. *Tetrahedron Lett.* **1974**, *36*, 3171−3174.

10.1021/jo034032r CCC: $25.00
Published on Web 04/16/2003

TABLE 1. Oxidation of Ketene Dithioacetals 3a−f

substrate	time (h)	yield[a] (%)	ee[b,c] (%)
3a	5.5	65	98[d]
3b	6	62	>99
3c	20	75	>99[e]
3d	24	73	>99
3e	21	71	>99
3f	18	60	>98[f]

[a] Isolated yield. [b] Enantiomeric excess determined by chiral HPLC (see the Supporting Information for details). [c] Absolute configurations of **4b** and **4d** were determined by comparison of $[\alpha]_D$ with the literature[6] and assigned (*R,R*). All others assigned by analogy. [d] Enantiomeric excess of monoxide **6a** was found to be 82% by chiral HPLC for the major geometric isomer. [e] Enantiomeric excess of monoxide **6c** was found to be 85% by chiral HPLC. [f] Enantiomeric excess was determined by NMR using the Pirkle chiral shift reagent. This represents the limits of detection of the other enantiomer by this method.

dithiane derivatives, and the results are presented in Table 1. We were delighted to find that good yields and essentially complete enantioselectivity were obtained with all substrates without exception. While we had previously employed chiral shift reagents to determine the enantiomeric excess, we discovered that excellent separation of the two enantiomers of the polar bis-sulfoxides could be achieved by chiral HPLC.

The reactions have to be carefully monitored to ensure maximum conversion of the mono-sulfoxide to the bis-sulfoxide with minimum over-oxidation to the sulfoxide−sulfone.

The oxidation of **3c**[10] was studied in more detail. At the end of the reaction, in addition to the bis-sulfoxide **4c**, the mono-sulfoxide **6c** was isolated in 7% yield and 85% enantiomeric excess. Based on our belief that the second oxidation would also occur with substantial reagent control and with minimal influence from the existing sulfoxide, we expected to find substantial quantities of the meso bis-sulfoxide. From the Horeau principle, we would expect to obtain 14% of the meso bis-sulfoxide if the second oxidation occurred with the same level of reagent control.[11] However, we were unable to isolate this material. A similar situation arose in the oxidation of 1,3-dithianes bearing ester and phosphonate moieties in the 2-position: the trans bis-sulfoxides were obtained with high enantiomeric excess but none of the meso isomers were isolated.[6,8] The bis-sulfoxides of these substrates are sensitive to acid-catalyzed decomposition via a Pummerer reaction, and in these cases, we assumed that the meso isomer decomposed more readily than the C_2 isomer as it is substantially more acidic.[12] However, this could not be a viable explanation in the current study

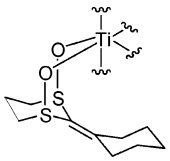
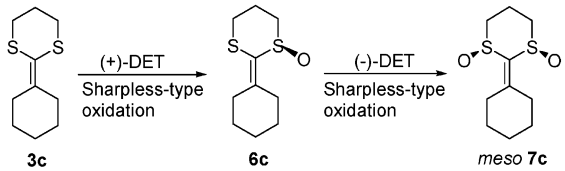


FIGURE 1. Meso bis-sulfoxide binding to titanium.

SCHEME 3. Proposed Synthesis of Meso Bis-sulfoxide 7c



as both the meso and C_2-symmetric bis-sulfoxides were expected to be equally stable, as there is no C-2 proton, and therefore, the bis-sulfoxides cannot decompose through an acid-catalyzed Pummerer reaction.

There are three possible explanations for the current observation: (1) the meso bis-sulfoxide is not formed to any appreciable extent because the stereochemistry of the initial sulfoxide does influence the second oxidation; i.e. the second oxidation is subject to both substrate and reagent control; (2) the meso bis-sulfoxide is oxidized to the sulfoxide−sulfone more rapidly than the C_2 isomer; or (3) the meso bis-sulfoxide acts as a bidentate ligand to titanium (Figure 1) and remains tightly bound even on workup.

Of the three possibilities, the first explanation seemed the more reasonable as the meso bis-sulfoxide had never been observed and only by leaving the reaction for extended periods of time was any of the sulfone−sulfoxide ever obtained. To determine which of the explanations was most likely, we attempted to prepare the meso bis-sulfoxide **7c**. However, treatment of **3c** with *m*-CPBA only gave the *dl* isomer **4c**, indicating that there was a substantial degree of substrate control in favor of the trans isomer. To prepare the meso compound, we therefore needed to control the second oxidation through reagent control. The Sharpless-type reagent employing (+)-DET showed a high degree of reagent control in the oxidation of dithiane **3c** to the (*R*)-mono-sulfoxide **6c** (ratio of *R*/*S* was 93:7). We reasoned that the meso isomer **7c** should therefore be favored by employing the opposite enantiomer of DET in the second oxidation, if reagent control was able to overcome substrate control (Scheme 3).

In the event, treatment of the (*R*)-mono-sulfoxide of 86% enantiomeric excess (obtained from (+)-DET) with the Sharpless-type reagent employing (−)-DET led to the trans bis-sulfoxide, but again without isolation of any of the meso isomer (Scheme 4). This indicates that substrate control dominates over reagent control in the second oxidation. However, we could not achieve complete mass balance and so the possibility remained that the meso isomer was formed but not isolated.

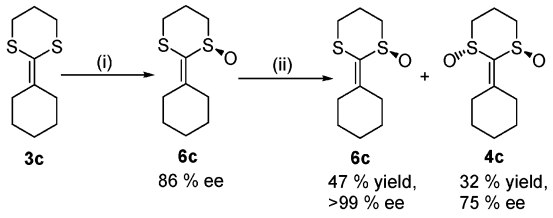
To test whether the second oxidation is subject to both substrate control and reagent control (Scheme 5), we decided to monitor the enantiomeric excess of the *mono-sulfoxide* **6c** over time. If no meso isomer is formed and

(10) This substrate was chosen to simplify the analysis, as no double-bond isomers of the mono-sulfoxide are possible.

(11) According to the x^2, y^2 rule (Horeau principle), the ratio of the enantiomers of the bis-sulfoxide should be close to the square of the enantiomers of the mono-sulfoxide in the asymmetric oxidation of bis-sulfides. The enantioselectivity of the mono-sulfoxide **6c** is 85%, so if this principle is followed then the expected enantioselectivity for the bis-sulfoxide would be 99.2%. This rule would also predict that there should be approximately 14% ($2xy$) of the meso bis-sulfoxide, assuming complete reagent control. For an explanation of the Horeau principle, see ref 8a and: Rautenstrauch, V. *Bull. Chim. Soc. Fr.* **1994**, *131*, 515−524.

(12) The C-2 proton of *cis*-1,3-dithiane 1,3-dioxide has a pK_a of 22.0, whereas *trans*-1,3-dithiane 1,3-dioxide has a pK_a of 24.9. See: Aggarwal, V. K.; Davies, I. W.; Franklin, R.; Maddock, J.; Mahon, M. F.; Molloy, K. C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2363−2368.

SCHEME 4. Oxidation of Mono-sulfoxide 6c with (−)-DET[a]



[a] Reagents and conditions: (i) $Ti(O^iPr)_4$ (0.5 equiv), (+)-DET (2 equiv), $PhC(Me)_2OOH$ (4 equiv), CH_2Cl_2, −40 to −20 °C; (ii) $Ti(O^iPr)_4$ (0.5 equiv), (−)-DET (2 equiv), $PhC(Me)_2OOH$ (4 equiv), CH_2Cl_2, −40 to −20 °C.

SCHEME 5. Proposed Route for Diastereo- and Enantioselective Oxidation of 3c to Trans Bis-sulfoxide 4c

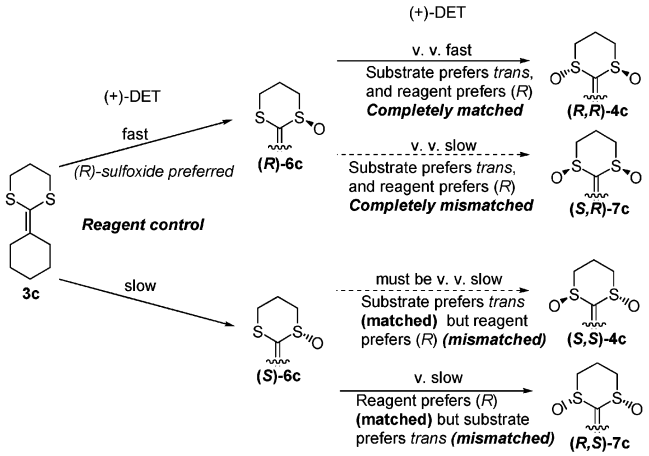


TABLE 2. Monitoring the Oxidation of 3c over Time (Conditions as in Table 1)

time (h)	mono-sulfoxide **6c** yield[a] (%), (ee, %)[b]	bis-sulfoxide **4c** yield[a] (%), (ee, %)[b]
0.5	65 (84)	4 (>99)
1	65 (88)	10 (>99)
4	65 (83)	12 (>99)
6	49 (86)	30 (>99)
14	36 (84)	50 (>99)
24	33 (80)	53 (>99)

[a] NMR yield. [b] Enantiomeric excesses were determined by chiral HPLC.

if the trans bis-sulfoxide **4c** is formed with very high enantiomeric excess, then in the second oxidation only the (*R*)-enantiomer of the mono-sulfoxide reacts with chiral oxidant to give the (*R*,*R*)-bis-sulfoxide **4c**. Thus, as the major (*R*)-enantiomer of the mono-sulfoxide **6c** is converted to the trans bis-sulfoxide **4c**, the enantiomeric excess of the remaining mono-sulfoxide **6c** should gradually decrease over time and eventually the mono-sulfoxide should be enriched in the (*S*)-isomer.

This experiment was therefore conducted (Table 2) but instead of a gradual decrease in enantioselectivity of the mono-sulfoxide **6c** over time, the enantioselectivity remained approximately constant! After 0.5 h, a 65% yield of mono-sulfoxide **6c** was obtained with 84% enantiomeric excess, and after 24 h, a 33% yield of mono-sulfoxide **6c** remained with 80% enantiomeric excess. If the reaction was conducted on a 100 g scale, after 0.5 h, 60 g of (*R*) and 5 g of (*S*) mono-sulfoxide **6c** were present, and after 24 h, 30 g of (*R*) and 3 g of (*S*) remained. While we know that the (*R*)-enantiomer was converted to the (*R*,*R*)-bis-sulfoxide, the loss of the (*S*)-enantiomer was a mystery.

The only explanation we can offer to account for this situation is that some meso bis-sulfoxide (*R*,*S*) is formed, but it forms a tightly bound complex with titanium (Figure 1) and so is never isolated. Our inability to achieve good mass balance (despite testing different workups, including using citric acid[13]) and the constancy of the enantiomeric excess of the monoxide over time support this view.

In conclusion, we have demonstrated that ketene dithioacetals can be selectively oxidized to the trans bis-sulfoxides in good yield with essentially complete control over enantioselectivity. We believe that the high diastereoselectivity observed is a consequence of tight binding with titanium of the small amount of the meso diastereomer formed, which effectively removes this isomer. This explanation could also account for the high enantio- and diastereoselectivities observed in the bis-sulfoxidations of other dithiane derivatives.

Experimental Section

General Procedures for the Synthesis of Ketene Dithioacetals 3a−e. 2-Cyclohexylidene-1,3-dithiane 3c. 2-Trimethylsilyl-1,3-dithiane (3.00 g, 15.63 mmol) was dissolved in THF (30 mL) under nitrogen with stirring. The solution was cooled to −78 °C, and *n*-BuLi (1.6 M solution in hexanes: 11.70 mL, 18.73 mmol) was added. The solution was allowed to warm to 0 °C over 5 h. The solution was re-cooled to −78 °C, and cyclohexanone (2.06 mL, 19.88 mmol) was added. The solution was allowed to warm to room temperature over 47 h. The reaction solution was poured onto H_2O (50 mL), extracted with CH_2Cl_2 (5 × 50 mL), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Purification by column chromatography, on SiO_2 (hexane/Et_2O, 1:0−0.9:0.1), afforded **3c** as a colorless solid (1.922 g, 61%): mp (EtOH) 94−94.5 °C (lit.[14] 91.5−93.5 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 1.55 (m, 6H), 2.13 (dtd, J = 6.0 Hz, J = 4.0 Hz, J = 2.0 Hz, 2H), 2.46 (m, 4H), 2.86 (ddd, J = 6.0, 4.0, 2.0 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.4, 26.8, 27.6, 30.5, 32.2, 114.0, 145.3; MS (EI) *m*/*z* 200 (M^+), 125, 84.

General Procedures for the Synthesis of Ketene Dithioacetal Dioxides 4. (1*R*,3*R*)-2-Cyclohexylidene-1λ^4,3λ^4-dithiane 1,3-Dioxide 4c. (+)-Diethyl tartrate (0.34 mL, 2.01 mmol) and titanium(IV) isopropoxide (0.15 mL, 0.50 mmol) were dissolved in CH_2Cl_2 (5 mL) at room temperature under nitrogen and stirred for 20 min. 2-Cyclohexylidene-1,3-dithiane was dissolved in CH_2Cl_2 (1.0 mL) and added to the reaction mixture, which was then cooled to −40 °C and stirred for 1 h. Cumene hydroperoxide (80%; 0.76 mL, 4.01 mmol) was added, and the mixture was stirred at −40 °C for 10 min and then allowed to stand at −20 °C for 22 h. Distilled water (0.36 mL) was added and the reaction mixture allowed to warm to room temperature with stirring for 1 h. The reaction mixture was filtered through a pad of Celite and washed well with CH_2Cl_2, and the solvent removed under reduced pressure. Purification by column chromatography on SiO_2 (hexane/Et_2O/EtOH, 1:1:0−0:1:0−0:1:1) afforded **4c** as a colorless solid (173 mg, 75%): mp (EtOH/hexane) 159.5−161 °C; $[\alpha]^{22}_D$ −21.5 (*c* 1.0, $CHCl_3$); IR (neat) 2919, 1042 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.69 (m, 2H), 1.75−1.88 (m, 4H), 2.53 (tt, J = 9.0 Hz, J = 5.0 Hz, 2H), 2.84

(13) Gao, Y.; Klunder, J. M.; Hanson, R. M.; Masamune, H.; Ko, S. Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765−5780.
(14) Hwu, J. R.; Taekyo, L.; Gilbert, B. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3219−3223.

(m, 4H), 3.39 (dt, J = 14.5 Hz, J = 5.0 Hz, 2H), 3.53 (dt, J = 14.5 Hz, J = 9.0 Hz, 2H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 7.5, 25.9, 28.2, 32.7, 40.3, 135.5, 168.9; MS (EI) m/z 232 (M^+), 215, 184; HRMS (EI) found m/z 232.0594 (M^+), $C_{10}H_{16}S_2O_2$ requires 232.0591.

Acknowledgment. We thank Degussa Fine Chemicals for a studentship to R.M.S., Gadjah Mada University, Yogyakarta, Indonesia, for a studentship to R., and Bristol University.

Supporting Information Available: Experimental details and spectroscopic data for the preparation of all compounds. Chiral HPLC data for appropriate compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034032R