Enantioselective Synthesis of Thiosulfinates and of Acyclic Alkylidenemethylene Sulfide Sulfoxides

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Enantioselectivities up to 75% have been found in the catalytic mono-oxidation of di-*tert*-butyl disulfide and related compounds as well as of ketene-*S,S*-acetals with an in situ generated chiral dioxirane. The effect of solvents on the enantiomeric excess has also been examined.

Introduction

tert-Butanesulfinamide (**1**) has proven to be a versatile chiral ammonia equivalent for the asymmetric synthesis of amines. Condensation of **1** (Figure 1) with a wide range of aldehydes and ketones provides *N*-sulfinyl imines in very high yields. The *tert*-butanesulfinyl group both activates these imines to attack by nucleophiles and behaves as a chiral-directing group to provide *N*-*tert*-butanesulfinylamine derivatives in high yields and with high diastereoselectivity. Removal of the *tert*-butanesulfinyl group under mild conditions cleanly provides the functionalized amines. In view of these features, **1** has enjoyed rapidly growing use both in academic laboratories and industry.[1]

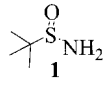

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Figure 1. *tert*-Butanesulfinamide.

Applications include the asymmetric synthesis of α-branched amines,[2] tertiary carbinamines,[3] highly substituted β-amino acids,[4] α-amino acids,[5] 1,2-amino alcohols,[6] and 1,3-amino alcohols.[7] In addition, *tert*-butanesulfinamide has been employed in a large number of drug discoveries and is used as the key chirality-bearing component of new classes of ligands for asymmetric catalysis.[8] Enantiomerically pure **1** was initially synthesized in two steps from the inexpensive petroleum byproduct di-*tert*-butyl disulfide (**2**) in 68% overall yield.[9] Asymmetric oxidation of **2** provided thiosulfinate (**3**) with high enantioselectivity and conversion using only 0.25 mol-% catalyst and with 30% hydrogen peroxide as an inexpensive, easy to handle oxidant. Although the reaction sequence is short and efficient and has enabled extensive use of the reagent, the oxidation of **2** to **3** needs several improvements to enable industrial-scale production of **1**. The enzymatic process constitutes a challenging approach; indeed, enantiomerically pure *tert*-butanethiosulfinate (**3**) can be obtained by oxidation of the corresponding disulfide **2** catalyzed by cyclohexanone monooxygenase (CHMO).[10]

Results and Discussion

The enantioselective oxidation of sulfides to sulfoxides is a well-studied reaction, in which a large variety of chemical oxidations have been used.[11]

In the light of the high stereoselectivity of the bovine serum albumin (BSA) catalysed oxidation of a wide range of sulfides,[12] we decided to investigate the possibility of using this chiral auxiliary for the preparation of chiral *tert*-butyl *tert*-butanethiosulfinate by the oxidation of **2** (Table 1) with different achiral oxidizing agents.

In all the experiments the only isolated product was the thiosulfinate **3** with no trace of the overoxidation product. However, its enantiomeric excess was low and for this reason, we decided to investigate another oxidizing system.

At first we considered the oxidation of *tert*-butyl disulfide using a chiral dioxirane in a two-phase system. This procedure could be included into catalysis by small organic molecules, termed organocatalysis, which recently has been getting increasing interest in organic synthesis. When com-

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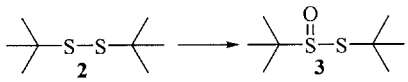
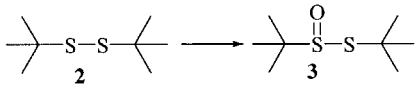
Table 1. Oxidation of *tert*-butyl disulfide in the presence of BSA.



Conversion[a] [%]	*ee*[b] [%]	Oxidizing Agent	Reaction Time [h]
72	8	$NaIO_4$	12
23	44	*tert*-BuOOH	12
17	12	$KHSO_5$	16

[a] The conversion was calculated by ^1H NMR spectroscopy. [b] Enantiomeric excess was determined by HPLC analysis using a chiral column.

Table 2. Oxidation of *tert*-butyl disulfide using the fructose derived dioxirane and $KHSO_5$.



Conversion[a] [%]	*ee*[b] [%]	Solvent	*T* [°C]
>98	72 (S)	CH_3CN/DMM (1:2)	20
>98	75 (S)	CH_3CN/DMM (1:2)	0

[a] The conversion was calculated by ^1H NMR spectroscopy. [b] Enantiomeric excess was determined by HPLC analysis using a chiral column.

pared to transition-metal-catalysed procedures, such reactions have advantages in terms of easy product purification and of their relative insensitivity to air and water, thus allowing for easier experimental execution.

The reaction conditions chosen were the same as used by Shi and coworkers for the epoxidation of a wide range of styrene derivatives, namely with the disulfide **2** (Table 2), ketone **4** and Oxone in a 1.0:0.30:1.38 molar ratio, respectively.[13] The fructose-derived ketone **4** (Figure 2) was used as chiral precursor and Oxone as achiral oxidant, which generate the chiral dioxirane in a catalytic cycle.

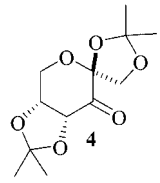


Figure 2. Fructose-derived ketone.

Screening of the solvent for the reaction was then undertaken, and the proper choice of solvents was found to be significant for obtaining good yields and enantioselectivities.

On the basis of these results, the mixed CH_3CN/DMM (dimethoxymethane) [1:2] was chosen as the reaction solvent for further studies (Table 3).

The disulfide **2** was completely oxidized to the corresponding thiosulfinate **3** with high enantiomeric excess (entry 1). The product was easily isolated from the reaction mixture by a simple extraction with petroleum ether, without need of further purification.

This favourable result led us to test the oxidation of disulfides **5**, **6** and of 1,3-dithiane **7** in the presence of the chiral dioxirane. The results obtained are listed in Table 4.

Table 3. Effect of solvents in the catalytic asymmetric oxidation of *tert*-butyl disulfide using the fructose derived dioxirane and $KHSO_5$.

Entry	Solvent	*t* [h]	Conversion [%]	*ee* [%][a]
1	CH_3CN/DMM (1:2)	1	>98	75
2	CH_3CN	1	>98	67
3	CMM	1	41	60.5
4	CH_2Cl_2	1	5	41

[a] Enantiomeric excess was determined by HPLC analysis.

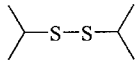
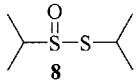
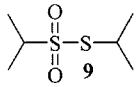
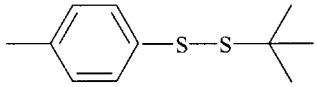
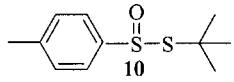
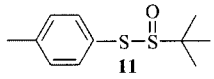
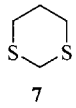
The low *ee* value for compound **8** is a consequence of the low optical stability of the product. Indeed, it has been reported that, apart from *tert*-butyl *tert*-butanethiosulfinate and diaryl thiosulfinate, the other thiosulfinates are optically unstable and racemize at room temperature.[10]

In contrast with the CHMO-promoted oxidation, which was completely regioselective,[10] in the case of compound **6** the fructose oxirane derivative led to a mixture of the two thiosulfinates **10**, **11** in a 2:1 ratio, with modest *ee*.

In the case of compound **7** the sulfoxide formed **12** was a racemic mixture, as a consequence of the direct oxidation of the substrate by Oxone; in fact, in the blank experiment carried out in the absence of ketone **4** the chemical yield did not change.

Another class of intriguing substrates to be explored in the context of chiral dioxirane-mediated oxidation is the family of acyclic alkylidenemethylene disulfides (S,S-ketene acetals), since the corresponding enantiopure disulfoxide congeners have been shown to be highly versatile partners for asymmetric synthesis.[14] Thus, we have examined the behavior of substrate **13** (see Table 5 and Scheme 1). In the presence of 2.1 equiv. of $KHSO_5$, a very clean reaction was observed with full consumption of starting material **13**. Monosulfoxide **14** was obtained as the major product, whose *E* stereochemistry was deduced from nOe studies.

Table 4. Oxidation of disulfide **5**–**7**.

Substrate	Product	Conversion [%][a]	*ee* [%][b]	*T* [°C]
 **5**	 **8**	90	35 (*S*)	0
	 **9**	10	–	0
 **6**	 **10**	66	34	0
	 **11**	32	5	0
 **7**	 **12**	18	0	0

[a] The conversion was calculated by ^{1}H NMR spectroscopy. [b] Enantiomeric excess was determined by HPLC analysis.

Minor disulfoxides **15** and **16** were also isolated. On two runs (entries 1 and 2), similar yields of products **15** and **16** with consistent *ee*s were recorded. In contrast with the behavior of 1,3-dithiane (**7**), partially soluble in the reaction medium, a blank experiment with no ketone **4** left starting material **13** untouched; this is possibly a consequence of the total insolubility and demonstrates the catalytic role of the ketone. Attempts to force the oxidation to produce **15** and/or **16** (entry 3) did not give a satisfactory result since the monosulfoxide **14** remained the major product. The poor solubility of **14** under the reaction conditions could be responsible for this failure. Moreover, when we changed the solvent (entries 4–6) conversion was low and *ee* even dropped in the case of dichloromethane (entry 6). This confirmed Shi's and our findings[13b] that a mixture of acetonitrile and dimethoxymethane is the best solvent for this reaction.

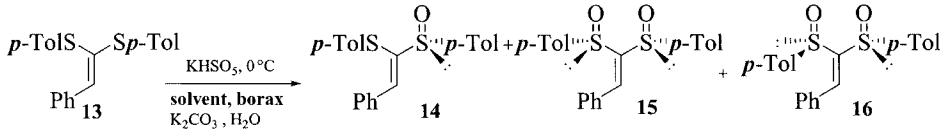
Conclusions

The chiral dioxirane oxidation appears to be a very promising tool for the asymmetric mono-oxidation of di-*tert*-butyl disulfide (**2**), as well as of the S,S-ketene acetal **13**.

Table 5. Oxidation of **13**.

Entry	Solvent	$KHSO_5$ [equiv.]	**14** Yield [%]; *ee* [%][a]	**15** Yield [%]; *ee* [%]	**16** Yield [%]; *ee* [%]
1	CH_3CN/DMM (1:2)	2.1	70; 43.9 (R_S)[b]	9; 36.5 (S_S,R_S)	18; 32.5 (R_S,R_S)
2	CH_3CN/DMM (1:2)	2.1	70; 46.1 (R_S)	8; 37.0 (S_S,R_S)	16; 31.5 (R_S,R_S)
3	CH_3CN/DMM (1:2)	6	30; 43.9 (R_S)	12; 16.1 (S_S,R_S)	14; 34.0 (R_S,R_S)
4	CH_3CN	2.1	30 (42); 38.2 (R_S)	nd	nd
5	DMM	2.1	14 (85); 43.0 (R_S)	nd	nd
6	CH_2Cl_2	2.1	4 (88); 30.4 (R_S)	nd	nd

[a] All *ee*s determined by chiral HPLC: CHIRALPAK AD-H or AD column. [b] Absolute configurations were deduced by comparison with enantiopure materials obtained by other synthetic methods. [c] Yield in parentheses corresponds to recovered starting material.



Scheme 1.

Totally unprecedented in this context, this organo-catalyzed oxidation has given highly encouraging *ee*s for **3** and for **14**, respectively, 75% and 46%. Further refinements of this process will include optimization of the structure of the ketone catalyst and reaction conditions, including scale up, as well extension to other sulfur-based substrates. Utilization of **14** as a Michael acceptor is also an intriguing possibility.

Experimental Section

General Remarks: Oxone and disulfides **2**, **5** and **7** were purchased from Aldrich. The fructose-derived ketone **4**[13b] and disulfide **6**[10] were synthesized according to known methodologies. S,S-ketene acetal **13** was prepared through the following sequence: alkylation of the lithium anion of bis(*p*-tolylthio)methane with benzaldehyde, acetylation and elimination by diazabicycloundecene (DBU). All glassware used for the oxidations was carefully washed to eliminate any trace metals in order to avoid the decomposition of Oxone.

The 300 MHz ^{1}H NMR spectra were measured on a Bruker AC 300 apparatus with $CDCl_3$ as solvent. HPLC analyses were performed on a Jasco HPLC instrument (model 980-PU pump, model 975-UV detector) using known conditions.[10] All reactions were monitored by analytical TLC on Merck silica gel 60 F_{254} plates and visualized by UV irradiation or by iodine.

General Procedure for Oxidation of 2 in the Presence of BSA: The disulfide **2** (1 mmol) and BSA (3.3 g, 5×10^{-2} mmol) were stirred magnetically in 12.5 mL of buffer solution for 2 h at 20 °C, then the relevant oxidant (1 mmol) was added, and stirring continued for an appropriate time. Extraction with four portions (60 mL each) of diethyl ether, and evaporation of the organic layer after drying with Na_2SO_4 gave the product **3**, which was analyzed by HPLC.

General Procedure for Oxidation of Disulfide 2, 5–7: The disulfide (1 mmol) was dissolved in the appropriate solvent (see Tables 2, 3 and 4) (15 mL). The buffer [10 mL, 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA)], tetrabutylammonium hydrogen sulfate (15 mg, 0.04 mmol) and ketone **4** (77 mg, 0.30 mmol) were added and the mixture was cooled to the appropriate temperature (Table 2). A solution of Oxone (0.85 g, 1.38 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 6.5 mL) and a solution of K_2CO_3 (0.8 g, 5.8 mmol) in water (6.5 mL) were added dropwise separately over a period of 1 h. After complete addition of Oxone, the reaction mixture was stirred for another 1 h and then extracted with petroleum ether (3×10 mL). The combined organic layers were dried with Na_2SO_4, filtered, and evaporated to yield the corresponding thiosulfinates, which were analyzed by HPLC.

Oxidation of 13: Ketene-S,S-acetal **13** (104 mg, 0.3 mmol) was dissolved in acetonitrile/ DMM (6 mL, 1:2, v/v). Subsequently buffer [3 mL, 0.05 M solution of $Na_2B_4O_7{\cdot}10H_2O$ in 4×10^{-4} M aqueous Na_2(EDTA)], tetrabutylammonium hydrogen sulfate (4 mg, 0.012 mmol) and ketone **4** (23 mg, 0.09 mmol) were added. A solution of Oxone (196 mg, 0.63 mmol) in aqueous Na_2(EDTA) (4×10^{-4} M, 3 mL) and a solution of K_2CO_3 (470 mg) in distilled water (3 mL) were added dropwise separately over a period of 45 min (by means of addition funnels). After completion of the addition, the reaction mixture was stirred for 15 min at 0 °C, diluted with water and extracted with dichloromethane. The combined extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by silica gel chromatography (pentane/ethyl acetate, from 100:0 to 50:50).

Determination of the Absolute Configuration of 14, 15 and 16: Absolute configurations of (*Rs*) **14**, (*Ss*, *Rs*) **15** and (*Rs*, *Rs*) **16** were determined by comparison with authentic samples made by other synthetic methods. (*Ss*) **14** was prepared in a two-step sequence: Enantiopure (*Rs*)-methyl sulfoxide was alkylated with *p*-tolyl disulfide in the presence of lithium diisopropyl amide (LDA). The resulting dithiane monoxide was then alkylated with benzaldehyde in the presence of triton B, giving (*Ss*) **14** with 94% *ee*. (*Ss*) **14** was then oxidized with *m*-chloro perbenzoic acid (MCPBA) and provided a mixture of the (*Rs*, *Ss*) antipode of **15** and of the (*Ss*, *Ss*) antipode of **16** which is known.[14a] Careful spectroscopic studies including MS ensured this assignment. All these data will be presented in a forthcoming article.

Acknowledgments

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[1] D. J. Weix, J. A. Ellman, *Org. Lett.* **2003**, *5*, 1317–1320 and references citated therein.
[2] G. Liu; D. A. Cogan, J. A. Ellman, *J. Am. Chem. Soc.* **1997**, *119*, 9913–9914.
[3] D. A. Cogan; G. Liu; J. A. Ellman, *Tetrahedron* **1999**, *55*, 8883–8904.
[4] T. P. Tang, J. A. Ellman, *J. Org. Chem.* **2002**, *67*, 7819–7832.
[5] D. D. Staas, K. L. Savage, C. F. Homnick, N. N. Tsou, R. G. Ball, *J. Org. Chem.* **2002**, *67*, 8276–8279.
[6] G. K. Prakash, M. Mandal, G. A. Olah, *Angew. Chem. Int. Ed.* **2001**, *40*, 589–590.
[7] T. P. Tang; S. K. Volkman, J. A. Ellman, *J. Org. Chem.* **2001**, *66*, 8772–8778.
[8] Z. Han, D. Krishnamurthy, D. Pflum, P. Grover, S. A. Wald, C. H. Senanayake, *Org. Lett.* **2002**, *4*, 4025–4028.
[9] D. A. Cogan, G. L. Liu, K. Kim, B. J. Backes, J. A. Ellmann, *J. Am. Chem. Soc.* **1998**, *120*, 8011–8019.
[10] S. Colonna, N. Gaggero, G. Carrea, P. Pasta, V. Alphand, R. Furstoss, *Chirality* **2001**, *13*, 40–43.
[11] M. Madesclaire, *Tetrahedron* **1986**, *42*, 5459–5495.
[12] a) S. Colonna, S. Banfi, F. Fontana, M. Sommaruga, *J. Org. Chem.* **1985**, *50*, 769–771; b) S. Colonna, N. Gaggero, *Tetrahedron Lett.* **1989**, *30*, 6233–6236; c) S. V. Dzyuba, A. M. Klibanov, *Tetrahedron: Asymmetry* **2004**, *15*, 2771–2777.
[13] a) Y. Shi, *Acc. Chem. Res.* **2004**, *37*, 488–496; b) Z. X. Wang, Y. Tu, Frohn, M. J. R. Zhang, Y. Shi, *J. Am. Chem. Soc.* **1997**, *119*, 11224–11235.
[14] For a review on the chemistry of disulfoxides, see: a) B. Delouvrié, L. Fensterbank, F. Nájera, M. Malacria, *Eur. J. Org. Chem.* **2002**, 3507–3525; b) F. Brebion, B. Delouvrié, F. Nájera, L. Fensterbank, M. Malacria, J. Vaissermann, *Angew. Chem. Int. Ed.* **2003**, *42*, 5342–5345.

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