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Highly enantioselective oxidation of cyclic dithioacetals by using a Ti(salen) and urea·hydrogen peroxide system

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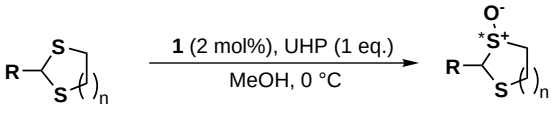
Abstract—Asymmetric oxidation of 2-substituted 1,3-dithianes using a Ti(salen) and urea·hydrogen peroxide system in methanol was found to proceed with high enantioselectivity to give the corresponding mono-sulfoxides.

Dithioacetal mono-oxides are umpolungs of carbonyl compounds, and their optically active derivatives serve as chiral masked acyl groups. Thus, much effort has been directed toward development of efficient methods for the preparation of optically active mono-oxides of cyclic dithioacetals such as 1,3-dithiolane and 1,3-dithiane.[1,2] Although many efficient asymmetric sulfoxidations have been reported, and some of them have been successfully applied to oxidation of cyclic dithioacetals (Scheme 1),[3–5] there is still room for improvement in terms of enantioselectivity and ecological acceptability. We recently reported a highly enantioselective sulfoxidation using di-μ-oxo Ti(salen) complex **1** as the catalyst in methanol (Scheme 2).[6] Complex **1** can be readily prepared by treatment of Ti(salen)Cl_2 with water and triethylamine[6,7] and further converted to the corresponding peroxo Ti(salen) **2** of *cis*-β structure when it is treated with hydrogen peroxide.[6,8] Complex **2** oxidizes various sulfides with high enantioselectivity. This reaction does not need a halocarbon solvent. To extend the utility of this reaction, we studied asymmetric oxidation of dithioacetals. In this paper, we describe our preliminary results on asymmetric mono-oxidation of 1,3-dithiolane and 1,3-dithiane.



Scheme 1.

We first examined oxidation of 2-phenyl-1,3-dithiolane and 2-phenyl-1,3-dithiane using complex **1** as the catalyst at 0°C. Both reactions proceeded smoothly with high enantioselectivity to give a single diastereomer, respectively. In particular, the reaction of 2-phenyl-1,3-dithiane showed excellent enantioselectivity of 99% ee. The absolute and relative configuration of both products was determined to be 1*S*,2*S* on the basis of ^{1}H NMR analysis and comparison of the specific rotations[9] (Scheme 3). The sense of enantiotopos selection in this reaction agreed with that observed in the oxidation of sulfides described in Scheme 2. Formation of the corresponding di-oxides was not detected.

We also examined oxidation of other substrates under the same reaction conditions (Table 1). In agreement with the above results, oxidation of 1,3-dithiane derivatives showed excellent and even somewhat better enantioselectivity than that of 1,3-dithiolane derivatives, except for the oxidation of 2-*t*-butylated substrates (entries 4 and 9). Oxidation of 2-(*t*-butyl)-1,3-dithiane showed only modest enantioselectivity (39% ee), while that of 2-(*t*-butyl)-1,3-dithiolane exhibited good enantioselectivity (84% ee). 2,2-Disubstituted cyclic dithioacetals are also good substrates for this reaction (entries 5 and 10). Diastereoselectivity of the reactions was also high. The relative configuration of the major products was not determined but assumed to be *trans* for steric reason.

Keywords: asymmetric catalysis; di-μ-oxo Ti(salen); sulfoxidation; dithioacetal; 1,3-dithiane.

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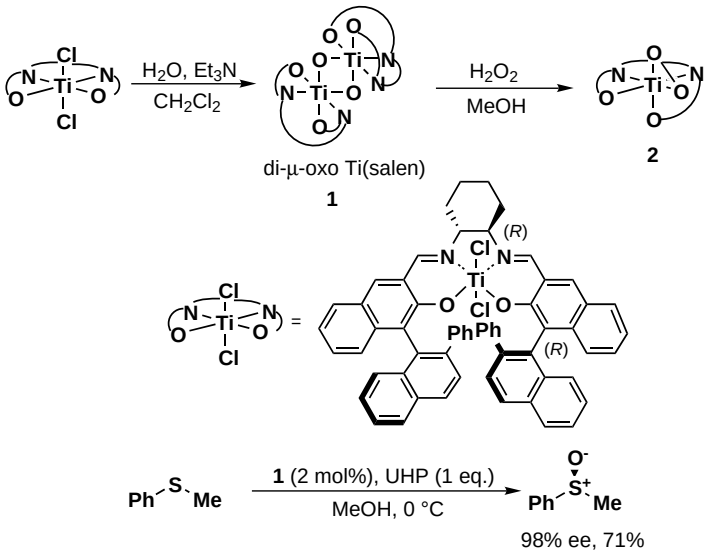
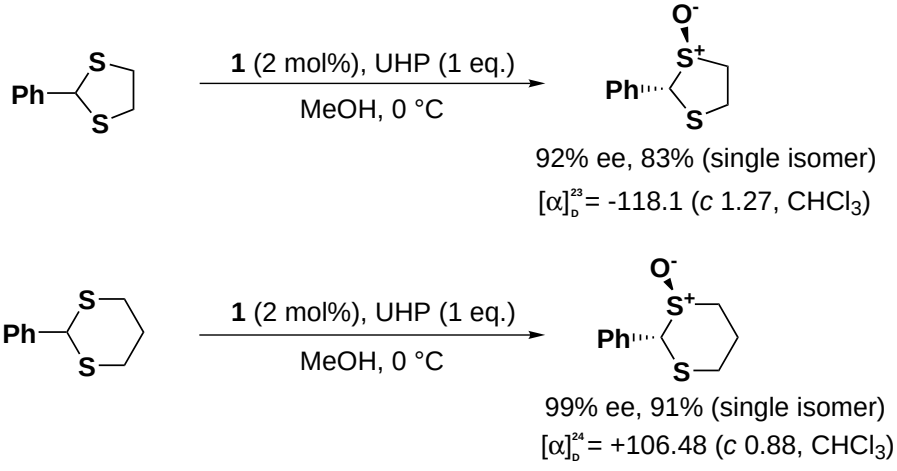


Scheme 2.



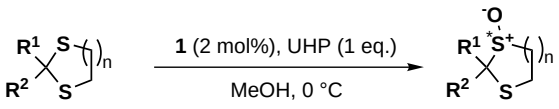
Scheme 3.

As we have already reported, the di-μ-oxo Ti(salen) and hydrogen peroxide system can be applied to oxidation of not only alkyl aryl sulfides but also dialkyl sulfides. In accord with this result, enantioselectivity of the present oxidation of cyclic dithioacetals using the same system was not affected by the electronic nature of the 2-substituent. For example, oxidation of 2-phenylethyl-1,3-dithiane showed an almost equal level of enantioselectivity to that of 2-phenylethynyl-1,3-dithiane (entries 7 and 8). Furthermore, in the oxidation of 1,3-dithiolane derivatives except for the oxidation of 2-(*t*-butyl)-1,3-dithiolane, enantioselectivity increased as the 2-substituent became large (entries 1–3 and Scheme 3). These stereochemical phenomena contrast with the stereochemistry of Mn(salen)-catalyzed epoxidation, in which the presence of an unsaturated olefinic substituent is essential for achieving high enantioselectivity.[10] Although the mechanism of asymmetric induction by Ti(salen) is unclear at present, the above difference is considered to be partly attributed to a different substrate-approaching manner in the two reactions: sulfides approach the peroxo species **2** along the O–O bond axis, while olefins approach the oxo Mn species from its side.[10]

Typical experimental procedure is exemplified by the oxidation of 2-phenyl-1,3-dithiane: To a solution of 2-phenyl-1,3-dithiane (19.6 mg, 0.1 mmol) in methanol (500 μl) was added complex **1** (3.6 mg, 2.0 μmol) and the solution was cooled to 0°C. To this solution was added urea·hydrogen peroxide adduct (9.4 mg, 0.1 mmol), and the mixture was stirred at the temperature for 24 h. The mixture was concentrated in vacuo and the residue was chromatographed on silica gel (hexane:ethyl acetate = 7:3–3:7–0:10) to give 2-phenyl-1,3-dithiane 1-oxide (19.3 mg, 91%). The enantiomeric excess of the sulfoxide was determined to be 99% ee by HPLC analysis using Daicel Chiralcel AD-H (hexane:*i*-PrOH = 3:1).

In conclusion, we were able to demonstrate that Ti(salen)-catalyzed asymmetric oxidation of sulfides

Table 1. Asymmetric oxidation of various cyclic dithioacetal using complex **1** as the catalyst



Entry	Substrate			Yield% (major and minor isomers)	d.r.[a]	% ee	
	R^1	R^2	n			Major	Minor
1	Bn	H	1	68	86:14	89[b]	88[b]
2	PhC_2H_4	H	1	75	87:13	88[c]	96[c]
3[d]	PhC≡C	H	1	89	99:1	79[e]	n.d.[f]
4	*t*-Bu	H	1	63	99:1	84[e]	n.d.[f]
5	Ph	Me	1	88	93:7	95[g]	91[g]
6	Bn	H	2	78	99:1	99[h]	n.d.[f]
7	$PhCH_2CH_2$	H	2	88	99:1	96[i]	n.d.[f]
8[d]	PhC≡C	H	2	88	90:10	95[j]	62[h]
9	*t*-Bu	H	2	82	94:6	39[e]	15[e]
10	Ph	Me	2	84	93:7	99[b]	22[b]

[a] d.r. = diastereomer ratio determined by HPLC analysis.
[b] Determined by HPLC using optically active column, Daicel Chiralcel OD-H (hexane:*i*-PrOH = 9:1).
[c] Determined by HPLC using optically active column, Daicel Chiralcel OJ-H (hexane:*i*-PrOH = 17:3).
[d] Due to poor solubility of the starting material to methanol, reaction was carried out in a 1:1 mixture of methanol and dichloromethane.
[e] Determined by HPLC using optically active column, Daicel Chiralpak AD-H (hexane:*i*-PrOH = 9:1).
[f] n.d. = not determined.
[g] Determined by HPLC using optically active column, Daicel Chiralcel OJ-H (hexane:*i*-PrOH = 3:2).
[h] Determined by HPLC using optically active column, Daicel Chiralpak AD-H (hexane:*i*-PrOH = 17:3).
[i] Determined by HPLC using optically active column, Daicel Chiralpak AD-H (hexane:*i*-PrOH = 4:1).
[j] Determined by HPLC using optically active column, Daicel Chiralcel OD-H (hexane:*i*-PrOH = 3:2).

using urea·hydrogen peroxide adduct as the oxidant was successfully applied to oxidation of cyclic dithioacetals.

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