Pergamon

Tetrahedron Letters 42 (2001) 3873–3876

TETRAHEDRON LETTERS

Ti(salen)-catalyzed enantioselective sulfoxidation using hydrogen peroxide as a terminal oxidant

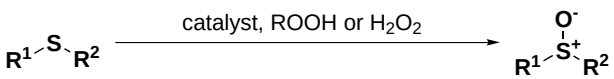
Bunnai Saito and Tsutomu Katsuki*

Department of Chemistry, Faculty of Science, Graduate School, Kyushu University 33, CREST, JST (Japan Science and Technology), Hakozaki, Higashi-ku, Fukuoka 812-8581, Japan

Received 14 March 2001; revised 2 April 2001; accepted 6 April 2001

Abstract—(*R*,*R*)-Di-μ-oxo Ti(salen) **4** was found to serve as an efficient catalyst for asymmetric oxidation of various sulfides with hydrogen peroxide. For example, oxidation of methyl phenyl sulfide by using **4** as the catalyst in the presence of a urea·H_2O_2 adduct showed high enantioselectivity of 94% ee. The high enantioselectivity of this reaction was considered to be related to the *cis*-β-structure of a monomeric Ti(salen) species generated from **4** in a methanol–hydrogen peroxide solution.

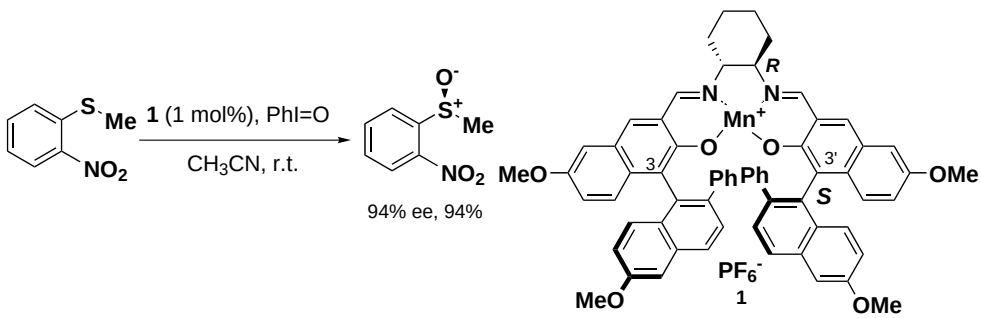
Optically active sulfoxides serve as various chiral auxiliaries in organic synthesis, and much effort has been directed toward the development of enantioselective sulfoxidation (Scheme 1).[1] Kagan et al.[2] and Modena et al.[3] have independently reported highly enantioselective sulfoxidation by using titanium–tartrate complexes modified with H_2O and tartrate as the catalyst, respectively. Various titanium–chiral diol complexes have also been reported to serve as the catalyst for enantioselective sulfoxidation.[4] Furthermore, (salen)–vanadium and –titanium complexes have been used as the catalyst.[5]



Scheme 1.

For these oxidations, alkyl hydroperoxides have been used as the terminal oxidant; however, use of hydrogen peroxide is desirable from the viewpoints of atom efficiency and ecological benignity. Jacobsen et al. reported that asymmetric oxidation of sulfides with hydrogen peroxide was catalyzed with modest enantioselectivity by using chloro(salen)manganese(III) complex as the catalyst.[6] Recently, Bolm et al. reported that a vanadium–chiral Schiff base complex served as the catalyst for asymmetric sulfoxidation, showing good enantioselectivity.[7,8] However, there is still room for improvement of the reaction especially in terms of enantioselectivity.

We recently reported that the second-generation (salen)manganese(III) complex **1** was an efficient cata-



Scheme 2.

Keywords: di-μ-oxo (salen)titanium complex; asymmetric catalysis; asymmetric sulfoxidation; sulfides; hydrogen peroxide.
* Corresponding author. Fax: +81 92 642 2607; e-mail: katsuscc@mbox.nc.kyushu-u.ac.jp

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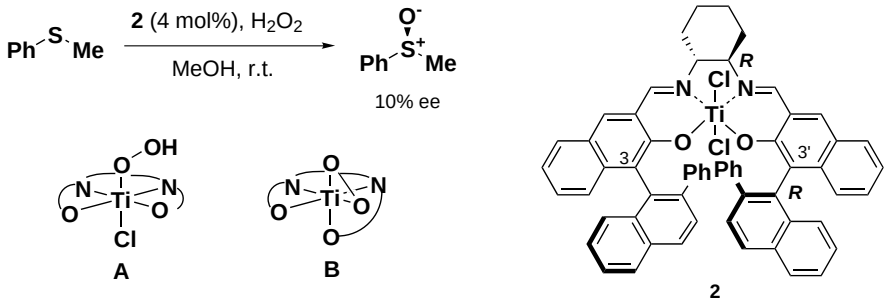
PII: S0040-4039(01)00590-1

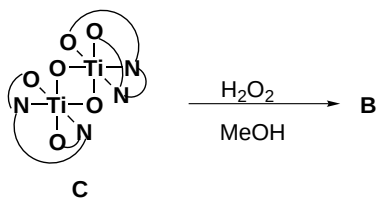


Scheme 3.

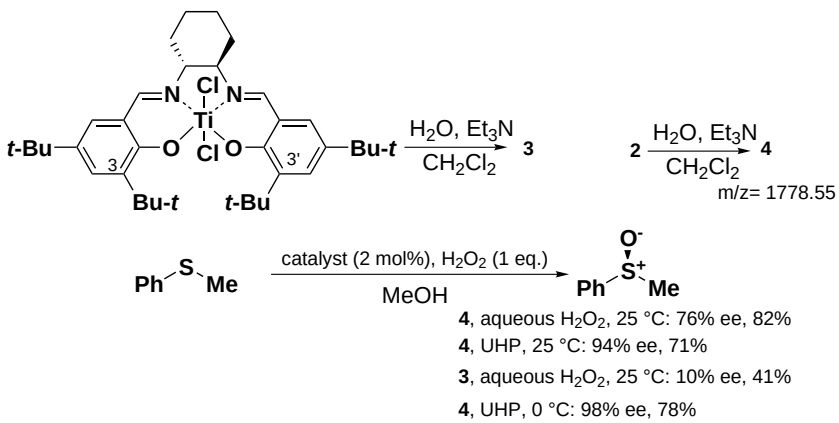
lyst for the asymmetric oxidation of alkyl aryl sulfides (Scheme 2) in which iodosylbenzene was used as the terminal oxidant.[9] However, the reaction with hydrogen peroxide as the terminal oxidant was sluggish.

To take advantage of the high asymmetry-inducing ability of second-generation (salen)manganese(III) complexes, we examined asymmetric oxidation using other metallosalen complexes as the catalyst and hydrogen peroxide as the terminal oxidant. Since Fujita et al. had reported that a (salen)titanium(IV) complex serves as the catalyst for asymmetric sulfoxidation,[5] we first examined the oxidation of methyl phenyl sulfide with the second-generation (salen)titanium(IV) complex **2** as catalyst and aqueous hydrogen peroxide in methanol (Scheme 3). However, only poor enantioselectivity was observed. Although the mechanism of this reaction was unclear, a hydroperoxotitanium species **A** was considered to be the active species, in which the salen ligand adopted a square-planar coordination and the hydroperoxo moiety has high conformational freedom. Accordingly, regulation of its conformation was considered to be indispensable for achieving high enantioselectivity. On the other hand, if the distal oxygen of the hydroperoxo moiety is coordinated to the titanium ion, the configuration of the moiety is fixed, though the salen ligand is forced to adopt a *cis*-β structure **B**.

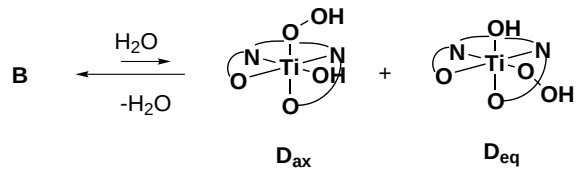
Recently, Belokon' et al. reported that a di-μ-oxo (salen)titanium complex, which served as an efficient catalyst for asymmetric hydrocyanation, had a *cis*-β dimer structure **C**.[10] We expected that complex **C** would give the desired **B** if it was treated with hydrogen peroxide in methanol (Scheme 4). Thus, we synthesized the di-μ-oxo species **3** according to the Belokon' procedure (Scheme 5). We also converted complex **2** to the corresponding di-μ-oxo (salen)titanium complex **4**, according to the same procedure. The formation of the di-μ-oxo species **4** was confirmed by FABMS analysis ($m/z = 1778.55$). With complex **4** in hand, we first examined oxidation of methyl phenyl sulfide. As we expected, the oxidation with aqueous hydrogen peroxide (31%) in the presence of **4** proceeded with good enantioselectivity of 76% ee. However, as the peroxo species **B** was considered to be equilibrated with hydroperoxo(hydroxo)titanium species **D** in the presence of water (Scheme 6), we next examined the oxidation with a urea·hydrogen peroxide adduct (UHP) in place of aqueous hydrogen peroxide. The reaction proceeded smoothly to give the sulfoxide in good yield with considerably improved enantioselectivity of 94% ee. The reaction with **3** as the catalyst was also exam-



Scheme 4.

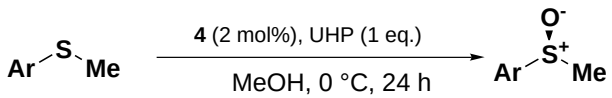


Scheme 5.



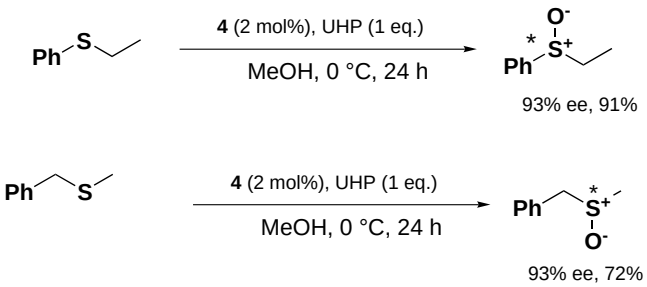
Scheme 6.

Table 1. Asymmetric sulfoxidation of methyl aryl sulfides by urea·hydrogen peroxide



Entry	Sulfide (Ar)	Yield (%)[a]	% ee
1	*p*-$MeOC_6H_4$	78	96[b]
2	*p*-BrC_6H_4	93	96[c]
3	*o*-BrC_6H_4	89	97[c]
4	*p*-ClC_6H_4	88	99[c]
5	*p*-$O_2NC_6H_4$	92	92[d]

[a] Isolated yield.
[b] Determined by HPLC analysis (Daicel Chiralcel OB-H, hexane/*i*-PrOH = 1:1).
[c] Determined by HPLC analysis (Daicel Chiralcel OB-H, hexane/*i*-PrOH = 4:1).
[d] Determined by HPLC analysis (Daicel Chiralcel OJ, hexane/*i*-PrOH = 7:3).



Scheme 7.

ined, but enantioselectivity was only modest. The reaction with **4** was further found to proceed with good enantioselectivity of 98% ee in an acceptable yield at 0°C. Use of other alcoholic solvents such as *i*-propanol and 2,2,2-trifluoroethanol reduced enantioselectivity as well as chemical yield.

Accordingly, we examined oxidation of substituted methyl phenyl sulfides with **4** as the catalyst in methanol at 0°C (Table 1). All the reactions proceeded with excellent enantioselectivity: the electronic nature and the position of the substituents had a minimal effect on the enantioselectivity (cf. entries 1 and 4 and entries 2 and 3). However, enantioselectivtiy was slightly reduced by introduction of a nitro group (entry 5).

Good substrates for this reaction were not limited to methyl aryl sulfides. Oxidation of ethyl phenyl sulfide and benzyl methyl sulfide was also smoothly effected under the same reaction conditions (Scheme 7).[11]

Preparation of (*R*,*R*)-di-μ-oxo complex **4** and typical experimental procedure for the oxidation of sulfides with **4** as the catalyst are described below.

Preparation of (*R*,*R*)-di-μ-oxo complex **4**: To a solution of complex **2** (262 mg, 0.27 mmol) in dichloromethane, were added two drops of water and triethylamine (77 μl, 0.54 mmol) and the mixture was stirred at room temperature overnight. The resulting pale yellow solution was washed with water, dried over magnesium sulfate, and concentrated in vacuo to yield complex **4** (167 mg, 69%) as a yellow solid.

Oxidation of *p*-chlorophenyl methyl sulfide (Table 1, entry 4): (*R*,*R*)-di-μ-oxo complex **4** (3.6 mg, 2.0 μmol) was dissolved in methanol and the solution was cooled to 0°C. To this solution were added urea·hydrogen peroxide (9.4 mg, 0.1 mmol) and subsequently *p*-chlorophenyl methyl sulfide, and the mixture was stirred at this temperature for 24 h. The mixture was concentrated in vacuo and the residue was chromatographed on silica gel (hexane:ethyl acetate = 1:1–3:7) to give *p*-chlorophenyl methyl sulfoxide (15.4 mg, 88%). The enantiomeric excess of the sulfoxide was determined to be 99% ee by HPLC analysis using Daicel Chiralcel OB-H (hexane:*i*-PrOH = 4:1).

In conclusion, we were able to demonstrate that (*R*,*R*)-di-μ-oxo Ti(salen) **4** served as an efficient catalyst for the asymmetric oxidation of sulfides with hydrogen peroxide as the terminal oxidant. The mechanism of the present reaction and the structure of the active peroxo titanium species are now under investigation.

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11. Enantiomeric excesses of the products were determined by HPLC analysis under the following conditions: Daicel Chiralcel OD-H, hexane/*i*-PrOH = 9:1 for ethyl phenyl sulfoxide, and Daicel Chiralcel OB-H, hexane/*i*-PrOH = 4:1 for benzyl methyl sulfoxide.