

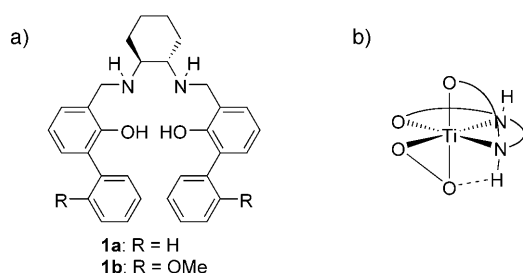
A μ -Oxo- μ - $\eta^2:\eta^2$ -Peroxo Titanium Complex as a Reservoir of Active Species in Asymmetric Epoxidation Using Hydrogen Peroxide**

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The development of efficient methods for preparing chiral epoxides with high optical purity is a topic of great importance in organic synthesis.^[1–3] As part of our studies on titanium-catalyzed asymmetric oxidation reactions using hydrogen peroxide as an oxidant,^[4–6] we recently reported that the readily available salan compound **1** serves as an effective ligand for the titanium-catalyzed asymmetric epoxidation of unfunctionalized olefins (Scheme 1a).^[7] On the

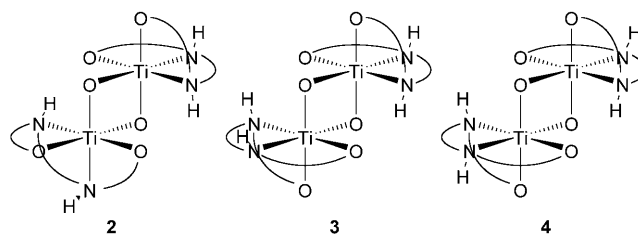
contrast in reactivities, the detailed reaction mechanism was unclear. Herein, we report the synthesis of an isolable μ -oxo- μ - $\eta^2:\eta^2$ -peroxo titanium complex that plays an important role as a reservoir of catalytically active species for asymmetric epoxidation.

We have reported that the premade di- μ -oxo titanium-(salan) catalyst with ligand *ent*-**1a** (the enantiomer of **1a**) and the catalyst prepared in situ from Ti(OiPr)₄ and salan *ent*-**1a** gave comparable yields and enantioselectivities in the asymmetric epoxidation of olefins, and the X-ray structure analysis of the di- μ -oxo complex with *ent*-**1a** revealed its homochiral structure, in which each *cis*- β titanium(salan) unit (in which one oxygen atom of the four coordinating atoms occupies an axial position) has the same chirality with respect to the titanium center (*anti*- Δ, R, R, S_N, S_N - Δ, R, R, S_N, S_N).^[7a,8] We have also found that the catalyst prepared in situ with salan **1b** showed a higher catalytic performance. Thus, we decided to evaluate the asymmetric catalysis of its di- μ -oxo titanium complex. Since ligand *ent*-**1a** resulted only in the di- μ -oxo complex with the (*anti*- Δ, R, R, S_N, S_N - Δ, R, R, S_N, S_N) configuration, we expected the production of a single isomer.^[9] Contrary to our expectations, however, salan **1b** resulted in three di- μ -oxo complexes (**2**, **3**, and **4**; Scheme 2), although



Scheme 1. a) Chiral salan ligand **1** for titanium-catalyzed asymmetric epoxidation. b) Proposed active species of titanium-catalyzed epoxidation. ONNO represents the backbone of the salan ligand.

other hand, the corresponding titanium(salan) complexes (in which double bonds replace the single bonds between the benzylic carbon atoms and the nitrogen atoms of the ligand) have been found to react with hydrogen peroxide to form a peroxo complex that is responsible for sulfide oxidation but is inert to olefin epoxidation. On the basis of these findings, we proposed that the titanium(salan) complexes provide more reactive peroxo species, which arise from a hydrogen bond between one of the peroxo oxygen atoms and the amino proton (Scheme 1b). Although the participation of the hydrogen-bonded peroxo species would explain the sharp



Scheme 2. Three isomers of di- μ -oxo titanium(salan) complexes with ligand **1b**.

complex **2** was the major product. Fortunately, each structure was unambiguously characterized by X-ray crystallographic analysis.^[10] While complex **2** has a homochiral (*anti*- Δ, S, S, R_N, R_N - Δ, S, S, R_N, R_N) configuration identical to the di- μ -oxo complex with **1a**, complexes **3** and **4** are pseudo-heterochiral, as the titanium centers in the two units have opposite chirality (*anti*- Δ, S, S, S_N, R_N - Δ, S, S, R_N, R_N for **3**; *anti*- Δ, S, S, S_N, S_N - Δ, S, S, R_N, R_N for **4**; see Figure 1 and Figures S1 and S2 in the Supporting Information). Complexes **3** and **4** differ in the stereochemistry of the chiral nitrogen atoms.

The catalytic performance of these complexes was evaluated using the reaction of 1,2-dihydronaphthalene with 30 %

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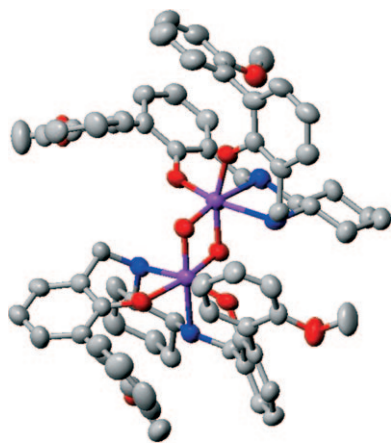


Figure 1. Crystal structure of homochiral di- μ -oxo titanium(salan) complex **2**. C gray, N blue, O red, Ti purple. Thermal ellipsoids are set at the 50 % probability level. Hydrogen atoms and noncoordinating solvent molecules are omitted for clarity.

hydrogen peroxide as the oxidant in phosphate buffer (pH 7.4) at 40 °C (Table 1). In our previous study, we reported that a combination of $\text{Ti}(\text{OiPr})_4$ and salan ligand *ent*-**1b** smoothly catalyzed the epoxidation in 99 % yield with 98 % *ee* (Table 1, entry 1).^[7c] The reaction with 0.5 mol % homochiral **2** furnished the epoxide with the same 98 % *ee* (Table 1,

Table 1: Asymmetric epoxidation of 1,2-dihydronaphthalene using titanium(salan) complexes.

Entry	Catalyst	Conv. [%] ^[a]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	$\text{Ti}(\text{OiPr})_4$ / <i>ent</i> - 1b ^[d]	99	99	98 (1 <i>S</i> ,2 <i>R</i>)
2	2 ^[e]	99	98	98 (1 <i>R</i> ,2 <i>S</i>)
3	3 ^[e]	> 99	99	98 (1 <i>R</i> ,2 <i>S</i>)
4	4 ^[e]	> 99	99	97 (1 <i>R</i> ,2 <i>S</i>)

[a] Determined by ^1H NMR spectroscopy (400 MHz). [b] Determined by ^1H NMR spectroscopy (400 MHz) with 2-bromonaphthalene as internal standard. [c] Determined by chiral HPLC analysis (Daicel Chiralcel OB-H; hexane/*i*PrOH = 99:1). [d] $\text{Ti}(\text{OiPr})_4$ /*ent*-**1b** = 1:1.3. [e] 0.5 mol % catalyst (1 mol % based on titanium).

entry 2). Almost identical enantioselectivity was also obtained in the reactions with heterochiral **3** and **4** (Table 1, entries 3 and 4). These results indicate that the same active species, probably a monomeric one, is generated in all cases.

To measure the relative catalytic activity of the complexes in more detail, olefin conversion was plotted against time for the epoxidation of 2-vinylnaphthalene using 0.2 mol % **2** and **3** (Figure 2).^[11] Surprisingly, the complexes gave different results. With homochiral **2**, the conversion follows a sigmoidal curve, and an induction period of about 1 h was observed. This induction period was not observed with heterochiral **3**. Thus, the initial reaction rate with complex **2** was slower than with complex **3**, but the ultimate conversion with complex **2** was higher than with complex **3**.

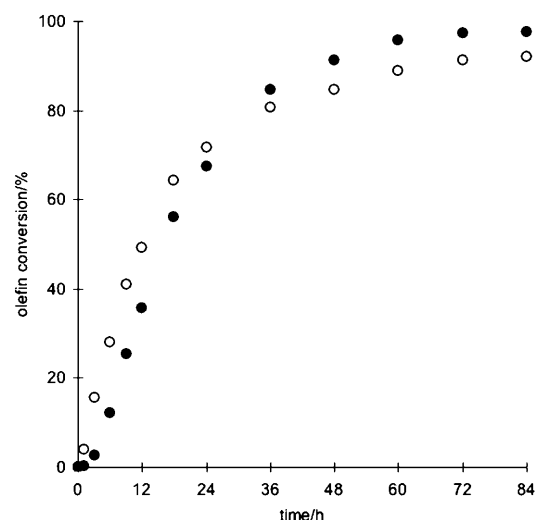


Figure 2. Time versus olefin conversion in the epoxidation of 2-vinylnaphthalene with 0.2 mol % di- μ -oxo titanium(salan) complexes **2** (●) and **3** (○). The reactions were conducted in 0.4 M olefin concentration at 25 °C. Each data point is an average of three runs.

When complex **2** was treated with 30 % hydrogen peroxide in the absence of olefin, the novel complex **5** was produced. While ^1H NMR spectroscopy and LC/ESI-MS analysis^[12] indicated that complex **5** might be a μ -oxo- μ -peroxo species, we eventually obtained a single crystal suitable for X-ray crystallography.^[10,13] The crystallographic analysis revealed that complex **5** displays a μ -oxo- μ -peroxo bridge, and the peroxo group bridges in a side-on mode, not an end-on mode (Figures 3 and 4).^[14,15]

The peroxo O–O bond length (1.449 Å) is almost identical to those of known η^2 -peroxo titanium complexes, but the Ti–O_{peroxo} bonds (2.017–2.051 Å) are longer.^[16] The short O–O bond implies a high energy barrier for olefin

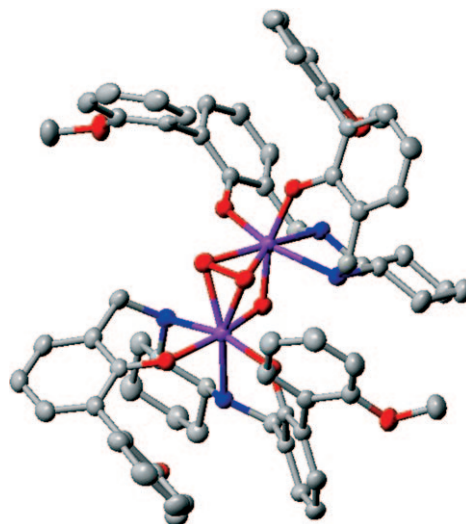


Figure 3. Crystal structure of μ -oxo- μ - η^2 : η^2 -peroxo titanium(salan) complex **5**. C gray, N blue, O red, Ti purple. Thermal ellipsoids are set at the 50 % probability level. Hydrogen atoms and noncoordinating solvent molecules are omitted for clarity.

epoxidation by O–O bond cleavage. Moreover, the crystal structure shows that hydrogen-bond formation between the peroxo oxygen atom and the amino protons, which we have proposed as an essential activation factor for epoxidation, is impossible in this dimeric structure. Indeed, no epoxidation event occurred when complex **5** was mixed with 1,2-dihydronaphthalene. However, the addition of aqueous hydrogen peroxide rendered it catalytically active. The epoxide was obtained in high yield and high enantioselectivity, which were almost the same to those obtained with the parent

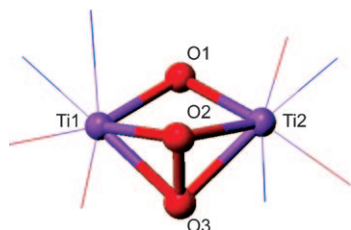
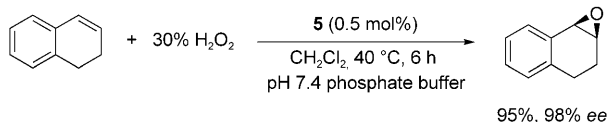


Figure 4. Bridging core structure of complex **5**. N blue, O red, Ti purple. Selected bond lengths [Å] and angles [°]: Ti1–O1 1.848(2), Ti1–O2 2.051(2), Ti1–O3 2.017(2), Ti2–O1 1.876(2), Ti2–O2 2.030(2), Ti2–O3 2.046(2), O2–O3 1.449(3); Ti1–O1–Ti2 98.09(11), Ti1–O2–Ti2 87.15(9), Ti1–O3–Ti2 87.61(9).

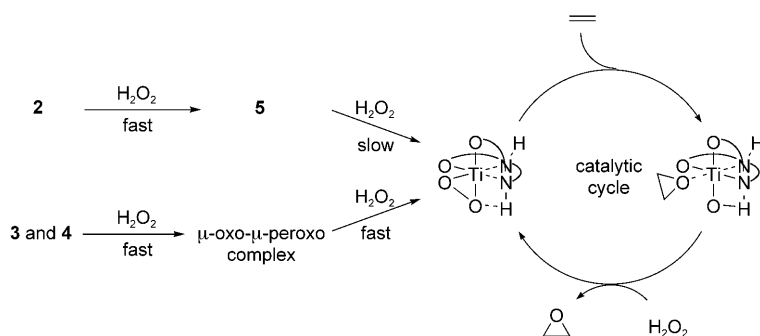
complex **2** (Scheme 3). This result clearly indicates that complex **5** is neither the real active species nor a dead-end species but an active intermediate. It is of note that an



Scheme 3. Asymmetric epoxidation with complex **5**.

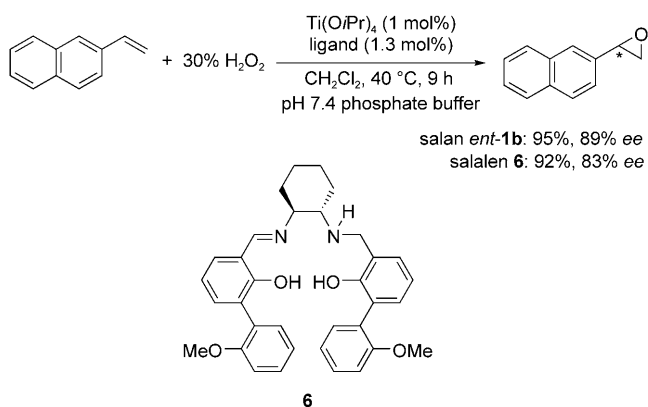
induction period was also observed in the epoxidation with complex **5**. On the other hand, treatment of heterochiral complex **3** with aqueous hydrogen peroxide or anhydrous urea–hydrogen peroxide adduct led to formation of a complex mixture. Considering these observations, it is feasible that the relatively stable μ -oxo- μ - η^2 : η^2 -peroxo complex **5** plays a key role as an active-species reservoir in the sense that it is slowly converted into an active species involved in the catalytic cycle and, thus, causes the induction period in the epoxidation with complexes **2** and **5** (Scheme 4). In contrast, decomposition of the μ -oxo- μ -peroxo complex derived from complex **3** is so fast that an induction period was not observed.^[17]

Recently, Berkessel et al. reported that treatment of a Ti(salalen) complex with hydrogen peroxide resulted in a secondary amine oxidation/dehydration sequence to give an inactive Ti(salen) complex.^[18] (Salalen is analogous to salen, but with one N–C_{benzyl} double bond.) We suspected that our Ti(salan) complexes were initially converted into the corre-



Scheme 4. A possible reaction pathway.

sponding Ti(salalen) complexes, which exhibit epoxidation catalysis. Therefore, we examined the epoxidation of 2-vinylnaphthalene using the catalyst prepared in situ from Ti(OiPr)₄ and salalen ligand **6**; the epoxide was obtained with lower enantioselectivity than in the corresponding reaction using salan ligand *ent*-**1b** (Scheme 5).^[7c] The clear difference



Scheme 5. Asymmetric epoxidation with Ti(OiPr)₄ and salalen **6**.

in the *ee* values suggests that a Ti(salan) complex is a real active species in the epoxidation using Ti(salan) complexes. It is worth noting that the enantioselectivity remained constant during the reactions with each complex. Although the participation of a Ti(salalen) complex in the epoxidation using Ti(salan) complexes cannot be completely ruled out at this stage, a monomeric Ti(salan) species is more likely to be the main contributor to this epoxidation catalysis.

In summary, we synthesized the μ -oxo- μ - η^2 : η^2 -peroxo titanium complex **5** using 30 % hydrogen peroxide. This study indicates that the complex serves as a reservoir of an active species and is slowly converted into an active species involved in the catalytic cycle of asymmetric epoxidation. We also revealed that the structure of the initial di- μ -oxo complexes significantly affects the catalytic performance. Further study on the reaction mechanism, particularly the catalytic cycle, is in progress.

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