Asymmetric Catalysis

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Titanium–Salan-Catalyzed Asymmetric Epoxidation with Aqueous Hydrogen Peroxide as the Oxidant**

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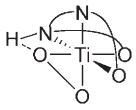
Oxidation reactions are at the core of methods for the conversion of bulk chemicals into useful and high-value materials.[1] Although many economical and highly selective methods for oxidation have been developed, more atom-efficient approaches that can be carried out under mild conditions are strongly desired from the viewpoint of protecting the environment and conserving resources. The choice of oxidant is an important factor in the enhancement of the efficiency of the oxidation reaction. Among the oxidants known, aqueous hydrogen peroxide is almost ideal, because it is relatively cheap, commercially available, and easy to handle; moreover, only water is generated as the by-product. Thus, the development of a catalyst for oxidation reactions with hydrogen peroxide has been a central theme in oxidation chemistry.[2] In particular, much effort has been directed toward the development of a chiral catalyst for epoxidation because of the high utility of optically active epoxides as versatile chiral building blocks.[3,4] However, a general and highly enantioselective epoxidation of unfunctionalized olefins with hydrogen peroxide has not been developed.

Recently, we developed a chiral di-μ-oxo titanium–salalen (salalen[5,6]: hybrid salan/salen tetradentate (ONNO)-type ligand; salan: *N*,*N*,-bis(*o*-hydroxybenzyl)-1,2-diaminoethane, salen: *N*,*N*'-bis(salicylidene)ethylenediamine) complex that was able to catalyze the epoxidation of unfunctionalized olefins using aqueous hydrogen peroxide with high enantioselectivity and a high turnover number of the catalyst.[7] The robustness and the unique catalysis of the titanium–salalen complex are in marked contrast with the ineffectiveness of the corresponding di-μ-oxo titanium–salen complex as an epoxidation catalyst. These distinctive features of the former complex have been attributed to hydrogen bonding between the amino proton and the oxygen atom of a putative peroxo species (Scheme 1). Although the complex is currently one of the most efficient catalysts for asymmetric epoxidation, it has a rather elaborate structure and its synthesis using Meerwein–Ponndorf–Verley reduction in situ has less flexibility in tuning the structure. Construction of an efficient catalyst that has a much simpler structure and that can be prepared from readily available compounds is a worthy challenge. A requirement for such a catalyst is the ability to efficiently enhance the reactivity of a putative peroxo species and to regulate its orientation in an asymmetric atmosphere. Thus, we newly introduced a series of di-μ-oxo titanium–salan complexes and examined their catalysis, because salan ligands and the corresponding titanium–salan complexes can be readily synthesized,[8] and the catalysis of the titanium–salan complex could be tuned by introducing an appropriate substituent to the ligand. Moreover, the complexes also possess amino protons to activate a putative peroxo species.



Scheme 1. A putative peroxo species activated by hydrogen bonding.

The experimental procedure for the synthesis of the di-μ-oxo titanium–salan complexes is shown in Scheme 2. Salan ligands **1a–d** were prepared by reduction of the corresponding salen ligands with $NaBH_4$. $[Ti(O\mathit{i}Pr)_4]$ was added to a solution of the salan ligand in dichloromethane, and subsequent treatment with water gave the di-μ-oxo titanium–salan complexes **2a–d**.[9]

First, asymmetric epoxidation of 1,2-dihydronaphthalene with 30% hydrogen peroxide in the presence of 5 mol% of a

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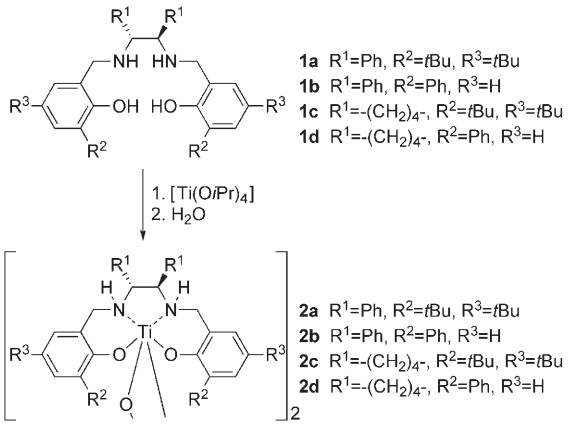
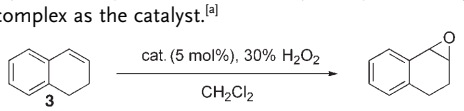


Scheme 2. Synthesis of di-μ-oxo titanium–salan complexes **2a**–**d**.

di-μ-oxo titanium–salan complex was investigated (Table 1). Titanium–salan complexes (**2a** and **2b**) with a diphenylethylenediamine moiety were found not to be efficient catalysts (entries 1 and 2). On the other hand, the complexes (**2c** and **2d**) bearing a cyclohexanediamine moiety showed the desired catalysis (entries 3 and 4). The presence of a cyclohexane ring was considered to provide a more suitable structure for hydrogen bonding of the amino proton with the oxygen atom of the peroxo group. Furthermore, introduction of a phenyl substituent at C3 and C3′ was found to remarkably enhance catalytic activity and improve enantioselectivity (entry 4). The use of 1.5 equivalents of hydrogen peroxide improved the yield to some extent (entry 5). Lowering the reaction temperature to 0 °C slightly increased enantioselectivity, although the yield was decreased somewhat (entry 6). Moreover, the catalyst prepared in situ from $[Ti(OiPr)_4]$ and ligand **1d** gave an almost comparable enantioselectivity to the pre-made catalyst **2d**, but slightly diminished yield was obtained (entry 7).[10] Although prolonged reaction time led to ring-opening of the epoxide to give a mixture of the corresponding 1- or 2-hydroperoxy 2- or 1-alcohol and 1,2-diol, the enantiomeric excess of the remaining epoxide did not change. Furthermore, when hydrogen peroxide was added to the reaction medium with a syringe pump over 4 h, a significant amount of ring-opened products was obtained (entry 8). These results suggested that **2d** decomposed under the reaction conditions into a Lewis acid complex that did not carry the salan ligand and did not promote epoxidation but ring-opening.

The substrate scope of the epoxidation using **2d** was investigated using 1.5 equivalents of hydrogen peroxide (Table 2). The epoxidation of terminal, *cis*-disubstituted, and trisubstituted olefins proceeded with high enantioselectivity. It is noteworthy that the epoxidation was stereospecific and no formation of the *trans* epoxide was detected in the epoxidation of *cis*-1-phenylpent-3-en-1-yne (entry 4). How-

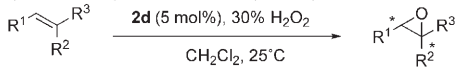
Table 1: Asymmetric epoxidation of 1,2-dihydronaphthalene (**3**) with a Ti–salan complex as the catalyst.[a]

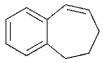
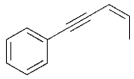
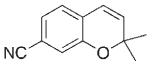
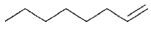


Entry	Catalyst	*t*	*T* [°C]	Yield [%][b]	*ee* [%][c]	Config.[d]
1	**2a**	24	25	NR		
2	**2b**	24	25	< 5	44	1*S*,2*R*
3	**2c**	24	25	19	82	1*S*,2*R*
4	**2d**	6	25	73	95	1*S*,2*R*
5[e]	**2d**	6	25	87	96	1*S*,2*R*
6[e]	**2d**	24	0	79	98	1*S*,2*R*
7[e]	**2d**[f]	6	25	80	94	1*S*,2*R*
8[e,g]	**2d**[h]	5	25	24 (30, 21)	95	1*S*,2*R*

[a] Reaction conditions: catalyst (5 μmol), 1,2-dihydronaphthalene (0.1 mmol), and aqueous H_2O_2 (30%, 0.12 mmol) in CH_2Cl_2 (1.0 mL). [b] Determined by ^1H NMR (400 MHz) spectroscopic analysis; the yields of the ring-opened products (1,2-diol, 1- or 2-hydroperoxy 2- or 1-alcohols) are given in brackets. [c] Determined by HPLC analysis on a chiral stationary-phase column (Daicel chiralcel OB-H, hexane/*i*PrOH = 99:1). [d] Determined by comparison of the elution order with that of the authentic sample in HPLC analysis. [e] Amount of aqueous H_2O_2 = 1.5 equivalents. [f] The catalyst was generated in situ. [g] Hydrogen peroxide was added with a syringe pump over 4 h. [h] Amount of complex **2d**: 3 μmol. NR = no reaction.

Table 2: Asymmetric epoxidation catalyzed by **2d**.[a]



Entry		Substrate	Yield [%][b]	*ee* [%]	Configuration[c]
1[d]	**4**		72	95[e]	1*S*,2*R*
2	**5**		44	97[f]	5*S*,6*R*
3	**6**		47	82[g]	*S*
4	**7**		69	90[h]	2*R*,3*S*
5	**8**		77	99[i]	3*S*,4*S*
6[d]	**9**		55	95[j]	1*R*,2*S*
7	**10**		25	55[k]	*R*

[a] Reaction conditions: catalyst **2d** (5 μmol), olefin (0.1 mmol), and aqueous H_2O_2 (30%, 0.15 mmol) in CH_2Cl_2 (1.0 mL) at 25 °C for 24 h. [b] Determined by ^1H NMR (400 MHz) spectroscopic analysis. [c] Determined by comparison of the elution order with that of the authentic sample in HPLC analysis and/or comparison of the chiroptical data with the literature value. [d] Reaction time was 5 h. [e] Determined by HPLC analysis on a chiral stationary-phase column (Daicel Chiracel OB-H; hexane/*i*PrOH = 90:10). [f] Determined by HPLC analysis on a chiral stationary-phase column (Daicel Chiralpak AS-H; hexane/*i*PrOH = 99.9:0.1). [g] Determined by HPLC analysis on a chiral stationary phase column (Daicel Chiracel OD-H; hexane/*i*PrOH = 99.9:0.1). [h] Determined by HPLC analysis on a chiral stationary phase column (Daicel Chiracel OD-H; hexane/*i*PrOH = 99:1). [i] Determined by HPLC analysis on a chiral stationary phase column (Daicel Chiracel OJ-H; hexane/*i*PrOH = 70:30). [j] Determined by HPLC analysis on a chiral stationary-phase column (Daicel Chiracel OB-H; hexane/*i*PrOH = 99:1). [k] Determined by ^1H NMR spectroscopic analysis using a chiral shift reagent [Eu(hfc)$_3$] (hfc = 3-(heptafluoropropylhydroxymethylene)-D-camphorate).

ever, the reaction of a nonconjugated terminal olefin was slow (entry 7).

The reaction mechanism is unclear at present. It is, however, of note that the catalyst prepared in situ from $[Ti(OiPr)_4]$ and an *N*,*N*′-dimethylated derivative of **1d** did not show any catalytic activity for the epoxidation of styrene. This result agreed with our proposal that a titanium–peroxo species is activated through hydrogen bonding. Moreover, when a solution of **2d** in dichloromethane was treated with aqueous hydrogen peroxide, a new species was obtained. Analysis by cold-spray ionization mass-spectrometry (CSI-MS) indicated a μ-peroxo-μ-oxo species ($M_r = 1097.3$); however, this species was also detected by CSI MS in the presence of hydrogen peroxide and 1,2-dihydronaphthalene. Accordingly, it is very likely that the active species is not the dimeric μ-peroxo-μ-oxo species but a monomeric peroxo or dimeric di-μ-peroxo species.

In summary, the titanium–salan-catalyzed asymmetric epoxidation of unfunctionalized olefins using aqueous hydrogen peroxide has been developed. High enantioselectivity of up to 98% *ee* was achieved for several olefins. We have demonstrated that a more efficient catalyst of lower molecular weight could be constructed for asymmetric epoxidation using hydrogen peroxide as the oxidant by appropriately considering the mechanism of activation of a peroxo species. Further improvements in the catalytic activity and detailed mechanistic studies are now in progress.

Experimental Section

2d: $[Ti(OiPr)_4]$ (1.3 mmol) was added to a solution of salan ligand **1d** (1.2 mmol) in dichloromethane (3.5 mL), and the solution was stirred at room temperature. A few drops of H_2O were added after 5 h, and the resultant mixture was stirred overnight. Volatiles were removed under reduced pressure, and the residue was recrystallized from dichloromethane to give the desired complex **2d** in 46% yield. Elemental analysis (%) for $C_{64}H_{64}N_4O_6Ti_2{\cdot}H_2O{\cdot}1.5\,CH_2Cl_2$: C 64.15, H 5.67, N 4.57; found: C 64.03, H 5.49, N 4.55; CSI MS: *m*/*z*: calcd for $C_{64}H_{64}N_4O_6Ti_2$: 1080.38; found: 1081.32 $[M^+ + H]$.

Typical procedure for epoxidation using a pre-made catalyst: Titanium complex **2d** (5 μmol) and 1,2-dihydronaphthalene (0.1 mmol) were dissolved in dichloromethane (1.0 mL) in an nitrogen atmosphere. The resultant mixture was stirred at room temperature after 30% aqueous hydrogen peroxide (0.15 mmol) had been added. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (pentane/Et_2O, 40:1) to give the corresponding epoxide. The *ee* value was determined by HPLC on a chiral stationary phase.

Typical procedure for epoxidation using a catalyst prepared in situ: Salan ligand **1d** (10 μmol) was added to a solution of $[Ti(OiPr)_4]$ (10 mmol) in dichloromethane (1.0 mL, 10 mM), and the solution was stirred at room temperature. A drop of water was added after 30 min, and the resultant mixture was stirred for 30 min. The reaction mixture was stirred at room temperature for 6 h after 1,2-dihydronaphthalene (0.1 mmol) and 30% aqueous hydrogen peroxide (0.15 mmol) were added. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel (pentane/Et_2O 40:1) to give the corresponding epoxide. The *ee* value was determined by HPLC on a chiral stationary phase.

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[9] CCDC-297268 (for complex **2d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[10] A catalyst prepared in situ from $[Ti(OiPr)_4]$ and a salan ligand with other substituents at C3 gave inferior results (H: 36%, 93% *ee*; Me: 69%, 93% *ee*; *t*Bu: 15%, 83% *ee*).

