Asymmetric Epoxidation

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Nb(salan)-Catalyzed Asymmetric Epoxidation of Allylic Alcohols with Hydrogen Peroxide**

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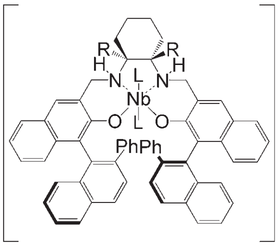
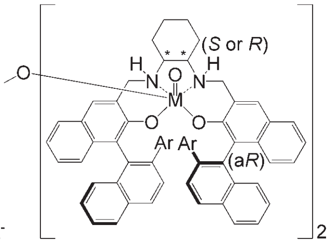
Optically active epoxy alcohols are versatile building blocks that are widely used in organic synthesis. Much effort has therefore been devoted to the development of efficient methods for their synthesis.[1] In 1980, Sharpless and one of the present authors (T.K.) reported a highly enantioselective and practical method for the asymmetric epoxidation of allylic alcohols using a titanium/tartrate/*tert*-butyl hydroperoxide system.[2] A catalytic version was also achieved by adding molecular sieves to the reaction system.[3] Basset and co-workers subsequently developed an efficient heterogeneous epoxidation of allylic alcohols using a silica-supported tantalum/tartrate complex as the catalyst,[4] and recently, Yamamoto et al. have made a major breakthrough by using a V/bis-hydroxamic acid/alkyl hydroperoxide system.[5,6] This latter system allows the use of aqueous *tert*-butyl hydroperoxide and can be applied to both allylic and homoallylic alcohols with high enantioselectivity,[5b,7] although an alkyl hydroperoxide must be used as the oxidant.

An important issue in current synthetic chemistry is the enhancement of ecological sustainability. In this light, the development of asymmetric oxidation using hydrogen peroxide, which is an atom-efficient and green oxidant, is a priority target in oxidation chemistry.[8] Consequently, various methods for asymmetric epoxidation with hydrogen peroxide have been reported. We recently discovered that di-μ-oxo Ti-(salalen)[9] and -(salan)[10] complexes are excellent catalysts for the epoxidation of simple olefins using aqueous hydrogen peroxide. These reactions have been proposed to proceed via a peroxo Ti species,[9–11] while the above metal-catalyzed oxidation of allylic alcohols has been proposed to proceed via an alkylperoxo metal species which is simultaneously coordinated by an allylic alcohol. Thus, these Ti(salalen) and -(salan) complexes cannot be applied to the epoxidation of allylic alcohols since the salalen or salan ligands are divalent and tetradentate. However, if the valence of the central metal ion of the salalen or salan complex is five or higher,[4] and if either the coordination number of the metal ion is larger than six or a donor atom of the ligand can dissociate reversibly, metal salalen or salan complexes should be catalysts for the epoxidation of allylic alcohols with hydrogen peroxide. It is known that salen complexes of zirconium and hafnium can adopt a seven-coordinate pentagonal-bipyramidal geometry[12] and that group 5 metals (Nb or Ta) are less oxophilic than group 4 metals. Hence, we were intrigued by the asymmetric epoxidation catalysis of Nb or Ta(salalen) and (salan) complexes. Herein we describe the Nb(salan)-catalyzed asymmetric epoxidation of allylic alcohols with hydrogen peroxide as the oxidant.

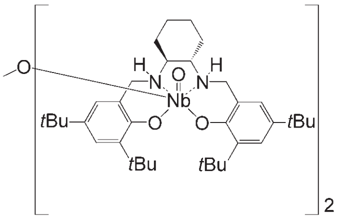
We first attempted to prepare the Nb and Ta(salan) complexes by mixing $Nb(OiPr)_5$ or $Ta(OEt)_5$ with a salan ligand in dichloromethane at room temperature. Mass spectrometric analysis indicated that the corresponding unstable monomeric complexes (e.g. **1**) were formed immediately[13] but that they slowly transformed into the more stable μ-oxo dimeric species, which were subsequently purified by silica gel chromatography.[14]



1: R=H, L = O*i*Pr
7: R=Me, L = O*i*Pr



2: (a*R*,*S*), M = Nb, Ar= Ph
3: (a*R*,*R*), M = Nb, Ar= Ph
5: (a*R*,*S*), M = Ta, Ar= Ph
6: (a*R*,*S*), M = Nb, Ar= 4-PhC_6H_4



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With the dimeric complexes **2**–**5** in hand, we examined the epoxidation of geraniol in the presence of four equivalents of urea–hydrogen peroxide adduct (UHP) at 20 °C in toluene (Table 1). Although epoxidation was found to be slow in the presence of **2**, it proceeded with a moderate enantioselectivity of 68 % *ee* (Table 1, entry 1). The reaction with complex **3** was slower and less selective (Table 1, entry 2). Complex **4** did not catalyze the reaction at all (Table 1, entry 3), whereas the reaction with Ta complex **5**, which carries the same ligand as **2**,

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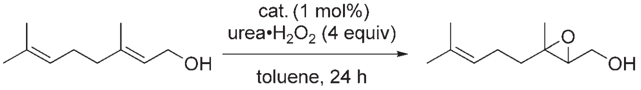
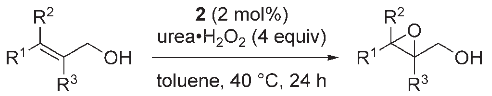
Table 1: Asymmetric epoxidation of geraniol catalyzed by dimeric Nb- and Ta(salan) complexes.[a]

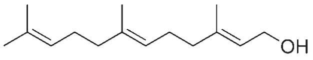
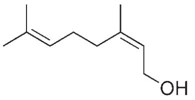
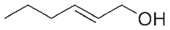
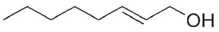
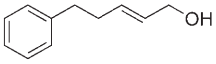
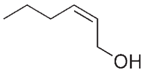
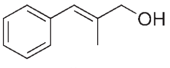
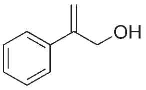


Entry	Cat.	Solvent	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**2**	toluene	20	24	68
2	**3**	toluene	20	10	−42
3	**4**	toluene	20	n.r[d]	–
4	**5**	toluene	20	13	42
5	**2**	toluene	40	61	81
6	**2**	toluene	60	32	67
7	**2**	CH_2Cl_2	40	22	68
8	**2**	THF	40	< 5	–
9	**2**	EtOAc	40	10	56
10	**2**	MeOH	40	40	*rac*
11[e]	**2**	toluene	40	83	81 (2*S*,3*S*)

[a] The reaction was carried out on a 0.5 mmol scale with catalyst (1 mol%) and UHP (4 equiv), unless stated otherwise. [b] Yield of isolated product after chromatographic purification. [c] Determined by HPLC analysis on a chiral phase (Daicel Chiralcel OB-H) after benzoylation. [d] No reaction. [e] Reaction performed with 2 mol% of **2**.

Table 2: Asymmetric epoxidation of various allylic alcohols with **2** as catalyst.[a]



Entry	Substrate	Yield [%][b]	*ee* [%][c]	Config.[d]
1		72	80[e]	2*S*,3*S*
2		66	80[e]	2*S*,3*R*
3		78	80[e]	2*S*,3*S*
4		81	79[e]	2*S*,3*S*
5		83	79	2*S*,3*S*
6		79	83[e]	2*S*,3*R*
7		86	72	2*S*,3*S*
8		83	68	2*S*

[a] The reaction was carried out on a 0.5 mmol scale with **2** (2 mol%) and UHP (4 equiv) at 40 °C. [b] Yield of isolated product after chromatographic purification. [c] Determined by HPLC analysis on a chiral phase. [d] Determined by comparison of the chiroptical data with the literature values. [e] Determined by HPLC analysis on a chiral phase after conversion into the corresponding benzoate.

was slower and less selective than that with **2** (Table 1, entry 4).[15]

We next optimized the reaction temperature for the epoxidation reaction with complex **2**, and found that a good enantioselectivity of 81% *ee* and acceptable chemical yields were obtained at 40 °C (Table 1, entry 5). The effect of solvent was also investigated at 40 °C, and toluene was found to be the solvent of choice in terms of enantioselectivity and yield (Table 1, entries 5 and 7–10). The epoxide was obtained in an acceptable yield when 2 mol% of **2** was used (Table 1, entry 11).[16]

The epoxidation of various allylic alcohols was examined under the optimized conditions (Table 2). The epoxidation of di- and trisubstituted olefins proceeded with a similarly good level of enantioselectivity to that of geraniol, irrespective of their geometry (Table 2, entries 1–6). However, the presence of a geminal substituent diminished the enantioselectivity to some extent (Table 2, entries 7 and 8). It is noteworthy that the present epoxidation is stereospecific.

Although we could not obtain a single crystal of complex **2**, we obtained a single crystal of complex **6**, the biphenyl derivative of **2**, which shows similar epoxidation catalysis behavior to **2**,[17] from a mixture of dichloromethane and diethyl ether (2:1). An X-ray structure analysis unambiguously showed its structure[18] to be that of an approximately C_2-symmetric oxo-bridged dimer (Figure 1).[19] Both Nb-(salan) units of **6** adopt a distorted octahedral configuration, and the chirality of the niobium-bound amine nitrogen atoms is *R*. It is noteworthy that the Nb(1)−O(4) distance is 1.744 Å, which suggests that this is a double bond. It should also be noted that the Nb(1)−O(1) bond is slightly shorter than the Nb(1)−O(2) and Nb(1)−O(3) bonds. Moreover, the N(3)−O(4) and N(1)−O(7) distances are as short as 2.824 and 2.902 Å, respectively, thereby indicating the presence of hydrogen bonding between the oxo oxygen and the amino hydrogen atoms. These two hydrogen bonds are likely to contribute to the stabilization of the oxo-bridged dimeric structure.

Complex **2** does not catalyze the epoxidation of simple olefins such as 1,2-dihydronaphthalene. The monomeric complex **1** is a poorer epoxidation catalyst with allylic alcohols due to slow transformation into **2**, although the enantioselectivity is only slightly reduced.[20] Moreover, complex **7**,[21] which is not converted into the corresponding dimer, does not catalyze the epoxidation of allylic alcohols at all. These results indicate that coordination of the allylic alcohol is essential for the epoxidation and that the active species is not a monomer but a dimer,[22] although the possibility that a monomeric Nb species catalyzes the epoxidation cannot be completely ruled out.

In summary, we have developed a novel dimeric oxo-bridged Nb(salan) complex that catalyzes the asymmetric oxidation of allylic alcohols using hydrogen peroxide as the oxidant. The X-ray analysis of **6** reveals its unique structure,[23] which is appropriately C_2-symmetric with both Nb(salan) units in a distorted octahedral configuration. To the best of our knowledge, the reaction reported herein is the first example of the asymmetric epoxidation of allylic alcohols with hydrogen peroxide. Further studies on the mechanism of this reaction are underway in our laboratory.

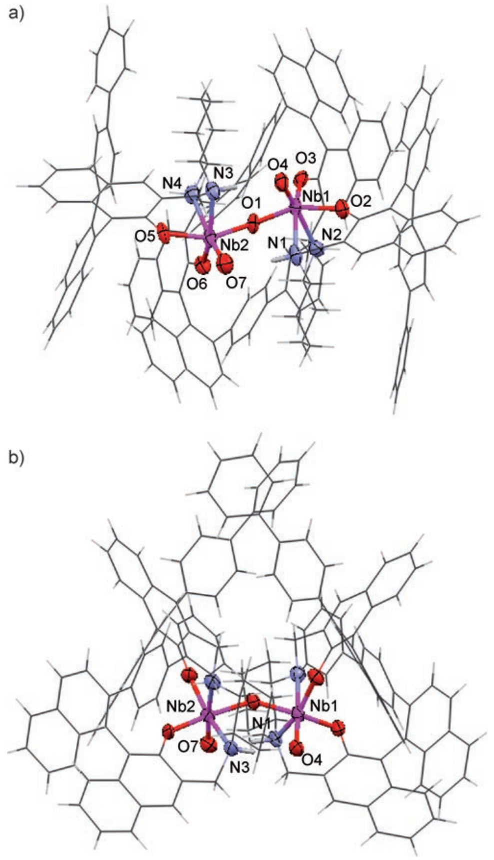


Figure 1. X-ray structure of **6**. a) Top view; b) side view.

Experimental Section

Typical procedure for the epoxidation of allylic alcohols: Nb(salan) complex **2** (18.9 mg, 2 mol %) and the allylic alcohol (0.5 mmol) were dissolved in toluene (1 mL). After stirring for 20 min at 40 °C, UHP (194 mg, 4 equiv) was added. The reaction mixture was stirred for 24 h then diluted with water (10 mL) and EtOAc (10 mL). The organic phase was separated and passed through anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by chromatography on silica gel (hexane/EtOAc 6:1) to give the corresponding 2,3-epoxy alcohol, which was dissolved in CH_2Cl_2. Triethylamine (1.1 equiv) and benzoyl chloride (1.1 equiv) were added to this solution. After 2 h, the reaction mixture was quenched with aqueous NH_4Cl and extracted with EtOAc. After removal of the solvent under reduced pressure, the residue was purified by chromatography on silica gel (hexane/EtOAc 9:1) to give the corresponding benzoate, the *ee* of which was determined by HPLC analysis.

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[13] The crude mixture was submitted for TOFMS analysis. **1**: TOFMS (ESI$^+$): *m*/*z* calcd for $[(C_{60}H_{48}N_2O_2)(C_3H_7O)_2Nb]$: 1039.3768; found 1039.3738.

[14] Complex **1** slowly transforms into the oxo-bridged dimeric complex **2** when left standing in air. The dissociation of **2** into **1** in dichloromethane or toluene solution was not observed by ^{1}H NMR spectroscopy or mass spectrometry. **2**: TOFMS (ESI$^+$): *m*/*z* calcd for $[C_{120}H_{96}N_4Nb_2O_7+H]^+$: 1892.5512; found: 1892.5524.

[15] The oxo-bridged dimeric Nb(salalen) complex was also prepared from the corresponding (a*R*,*S*,*S*,a*R*)-salalen ligand in the same manner and was used as a catalyst for the epoxidation of geraniol with UHP. Its catalytic activity was found to be poor.

[16] Oxidation with aqueous hydrogen peroxide was also examined at 40 °C but was found to be inferior to the reaction with UHP in terms of enantioselectivity and yield (40 % *ee*, 38 % yield for the epoxidation of geraniol).

[17] The epoxidation of geraniol using **6** as the catalyst gave the (2*S*,3*S*)-epoxide with 79 % *ee*.

[18] CCDC 677278 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.

[19] The median falling on the segment O_4–O_7 of the triangle defined by O_1, O_4, and O_7 is the axis of C_2 symmetry.

[20] The epoxidation of geraniol with in situ-prepared **1** (4 mol %) under the optimized conditions gave the corresponding epoxide with 74 % *ee* and 42 % yield.

[21] Complex **7** was prepared in situ because it is sensitive to water. **7**: TOFMS (ESI$^+$): *m*/*z* calcd for $[(C_{62}H_{52}N_2O_2)(C_3H_7O)_2Nb]$: 1067.4081; found: 1067.4061.

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