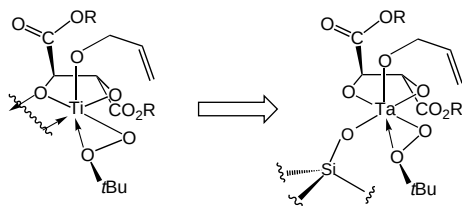


Silica-Supported Tantalum Catalysts for Asymmetric Epoxidations of Allyl Alcohols

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Asymmetric epoxidation of allyl alcohols is an important reaction in synthetic organic chemistry.^[1, 2] Katsuki and Sharpless^[3] have provided a successful solution which is now used for industrial applications.^[4] Although this catalytic process seems to be well understood,^[5–8] a heterogeneous system would be advantageous.^[9] It could avoid a complicated separation of product from catalyst, which can lead to decomposition of the epoxide formed.^[6–8]

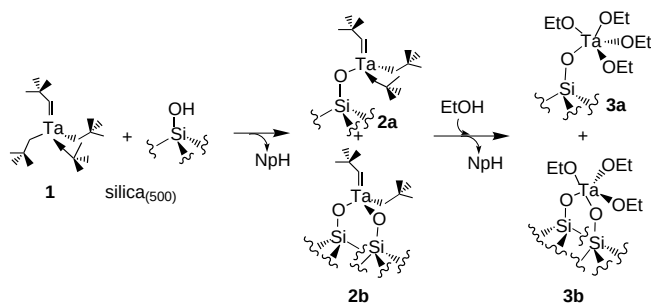
Several oxide-supported titanium compounds were prepared for catalytic epoxidations of allyl alcohols.^[10–13] However, the enantioselectivity was not reported, the metal may leach from the support, or the preparation of the solids seems to be difficult to reproduce.^[9] The choice of titanium to graft a Sharpless-type catalyst is perhaps not the right one, since the mechanism usually accepted requires a coordination sphere in which the four d electrons of Ti are involved in σ bonds with a tartrate group chelating the metal through two σ -bonded oxygen atoms, an allyl alkoxy group, and a σ/π -coordinated *tert*-butyl peroxy group (Scheme 1).^[5] If Ti^{IV} is grafted through one Si–O–Ti bond, then it cannot accommodate all these ligands. However, a Group 5 metal should be a potential active site.



Scheme 1. Left: Coordination sphere of titanium proposed by Sharpless et al.^[5] for the active sites in asymmetric epoxidations of allyl alcohols (only half of a dimer is shown). Right: Hypothetical coordination sphere of tantalum for a potential silica-supported active site.

Tantalum, which exhibits a low activity in homogeneous catalysis,^[1] could thus be a good candidate for such heterogeneous catalysis. We report here results which demonstrate that silica-supported tantalum species lead to active catalysts for these asymmetric epoxidations.

Silica-supported tantalum ethoxides were prepared in two steps (Scheme 2). The first step consists of grafting $\text{Ta}(\text{=CHCMe}_3)(\text{CH}_2\text{CMe}_3)_3$ (**1**) onto $\text{silica}_{(500)}$.^[14] Two surface tantalum species are then obtained: **2a** (ca. 50%), which is grafted to silica by one Si–O–Ta bond, and **2b** (ca. 50%), which is grafted by two such bonds.^[15] The second step consists



Scheme 2. Preparation of silica-supported tantalum alkoxides. NpH = Neopentane.

of exchanging the alkyl and alkylidene ligands of **2a** and **2b** with ethanol in order to obtain surface alkoxy–tantalum complexes **3a** and **3b**.^[16] We refer to the solids prepared in this way as [Ta]#1–[Ta]#3.^[17] A titanium catalyst, [Ti], was similarly prepared from $\text{silica}_{(500)}$ and $\text{Ti}(\text{OiPr})_4$ (1.8 wt % Ti).

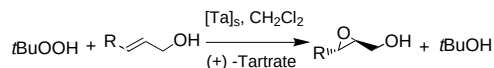
These tantalum- and titanium-containing solids were then used as catalysts for the asymmetric epoxidation of 2-propen-1-ol and *trans*-2-hexen-1-ol. The results, obtained after 48 h of reaction, are presented in Table 1. As already observed by Sharpless,^[7] when associated to (+)-diisopropyl tartrate ((+)-DIPT), $\text{Ti}(\text{OiPr})_4$ leads to an active and enantioselective catalyst for epoxidation of 2-propen-1-ol into (*S*)-glycidol (Table 1, entry 1; turnover number (TON) = 15 mol of glycidol produced per mol of titanium, 80% *ee*). The grafted titanium species in [Ti] leads to a poorly active catalyst and exhibits nearly no enantioselectivity (entry 2). Molecular $\text{Ta}(\text{OEt})_5$ does not lead to an active catalyst (entry 3), and the opposite enantiomer, (*R*)-glycidol, is obtained predominantly. Interestingly, upon use of the silica-supported tantalum species [Ta]#1–[Ta]#3, good activity and enantioselectivity are observed with molecular sieves (entry 4; TON = 28 mol of glycidol produced per mol of surface tantalum, 85% *ee*) or without molecular sieves (entry 5; TON = 15, 84% *ee*); the major enantiomer is (*S*)-glycidol. As expected, with the opposite tartrate, (–)-DIPT, the same results are obtained, but (*R*)-glycidol is the major product (compare entries 5 and 6).

The results show that the activity of silica-supported tantalum is due to surface sites and not to dissolved species since 1) molecular $\text{Ta}(\text{OEt})_5$ leads to almost inactive species with the major formation of the opposite enantiomer; 2) the chemical analysis (Ta or Ti) of the final solution and of the solids before and after reaction does not indicate any metal leaching (less than 2% of the supported metal); and 3) when the solid catalyst was isolated by filtration before the introduction of the last reactant, *tert*-butyl hydroperoxide (TBHP) or 2-propen-1-ol, as recommended by Sheldon et al.,^[18] the solutions were found to be inactive.

A precise comparison of the turnover frequencies (TOF) obtained for the molecular Ti catalyst and for the supported Ta species is not possible since we do not have enough kinetic data. Furthermore, we were not able to synthesize glycidol under experimental conditions similar to usual Sharpless conditions (0.5 M alcohol with a metal/substrate ratio of 5/100).^[7] It is difficult to work with concentrations higher than

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Table 1. Catalytic asymmetric epoxidation of allyl alcohols such as 2-propen-1-ol ($R = H$) and *trans*-2-hexen-1-ol ($R = nPr$) with solid tantalum catalysts $[Ta]_5$ or with molecular compounds, $Ti(OiPr)_4$ and $Ta(OEt)_5$.



Entry	Catalyst	R	Metal/alcohol ^[a]	Alcohol concentration	Conversion [%] ^[b]	Yield [%] ^[b]	ee [%] ^[b, c]
1	$Ti(OiPr)_4$	H	5/100	1.0 M ^[d, e]	76	72	80 (S)
2	[Ti]	H	5/100	0.4 M ^[d, e]	17	14	ca. -9 (R)
3	$Ta(OEt)_5$	H	2/100	1.0 M ^[d, f]	ca. 0.5	0.4	-45 (R)
4	[Ta]#2	H	2/100	0.1 M ^[d, f]	60	56	85 (S)
5	[Ta]#1	H	2/100	0.1 M ^[f]	31	30	84 (S)
6	[Ta]#1	H	2/100	0.1 M ^[g]	30	29	-83 (R)
7	[Ta]#3	H	2/100	0.4 M ^[f]	20	19.5	94 (S)
8	[Ta]#1	H	19/100	0.1 M ^[f]	79	77	84 (S)
9	$Ti(OiPr)_4$	<i>nPr</i>	5/100	1.0 M ^[d, h]	99	80	96 (S,S)
10	[Ta]#2	<i>nPr</i>	4/100	0.1 M ^[d, f]	48	40	90 (S,S)
11	[Ta]#2	<i>nPr</i>	4/100	0.1 M ^[h]	35	34	89 (S,S)
12	[Ta]#2	<i>nPr</i>	4/100	0.1 M ^[h, i]	35	31	93 (S,S)

[a] Molar ratio. [b] Determined after 48 h by GC (Lipodex E) with *n*-dodecane as an internal standard. [c] The major enantiomer obtained is shown in parentheses. [d] With 3-Å powdered molecular sieves previously dehydrated at 300 °C under vacuum. [e] At 0 °C; chiral inducer: (+)-DIPT; oxidant: CHP. [f] At 0 °C; chiral inducer: (+)-DIPT; oxidant: TBHP. [g] As in entry 5, but with (-)-DIPT. [h] At -20 °C; chiral inducer: (+)-DET; oxidant: TBHP. [i] As in entry 11, but with second use of the catalyst.

0.1 M while using a metal/substrate ratio of 2/100, because with the solid catalyst the reaction medium is too thick and more difficult to stir. Indeed, with a solid Ta catalyst, an increase in the alcohol concentration leads to lower alcohol conversion and yield, probably owing to the insufficient stirring, but the enantiomeric excess is better (94 % ee) and does not seem to be related to a subsequent kinetic resolution (compare entries 4 and 7). An increase in the metal/substrate ratio from 2/100 to 19/100 leads to a better yield, though the yield is not proportional to the amount of tantalum introduced (compare entries 4 and 8). The termination of the reaction may be explained by a poisoning of the catalytic sites either by water generated in side reactions or by a chelating diol produced in the ring opening of glycidol by an alcohol or water.^[6]

Silica-supported tantalum also showed good activity and enantioselectivity for the epoxidation of *trans*-2-hexen-1-ol to (2*S*,3*S*)-2-hydroxymethyl-3-propyloxirane with molecular sieves (Table 1, entry 10; TON = 10, 90 % ee) or without molecular sieves (entry 11; TON = 8.5, 89 % ee). For this substrate, homogeneous catalysis with molecular $Ti(OiPr)_4$ was very effective and enantioselective (entry 9; TON = 16, 96 % ee). The solid used in entry 11 was washed with CH_2Cl_2 after reaction and reused for a new reaction without adding tartrate. This preliminary result shows that the catalyst can be recycled and that almost the same results are obtained (entry 12; TON = 8, 93 % ee).

For these epoxidations, the surface tantalum and the Sharpless molecular titanium species both present good enantioselectivity and activity. The solid tantalum catalysts are easily separated from the reaction medium by filtration and can be recycled. The good catalytic activity observed for the solids containing tantalum and the bad performances of the silica-supported titanium catalyst are in good agreement with our conceptual approach (Scheme 1). The activity of

supported tantalum may result from the presence of well dispersed monomeric tantalum species on the silica surface, which would lead to monomeric active sites. The molecular tantalum alkoxides, $Ta(OR)_5$, which are dimers in weakly polar solvents^[19] would lead to dimers in the presence of tartrate and the reactants, as was proposed in the case of titanium.^[5] These molecular tantalum dimers would be poor active sites compared to supported monomeric species. Another important difference is the connection with the surface, which may also provide an activation of the catalytic site through the support.

Experimental Section

$Ta(=CHCMe_3)(CH_2CMe_3)_3$ (**1**) was prepared as described by Schrock et al.^[20] The silica used is an aerosil 200 from Degussa. It was activated at 500 °C under vacuum (10^{-4} mbar) and is referred to as silica₍₅₀₀₎. Diethyl (DET) and diisopropyl tartrates (DIPT) were available from Aldrich. Anhydrous *tert*-butyl hydroperoxide (TBHP) in dichloromethane was prepared by azeotropic distillation (70 % TBHP in water, Aldrich).^[7] All operations were carried out under an inert atmosphere (argon or vacuum). A solution of **1** in *n*-pentane was used to impregnate silica₍₅₀₀₎. The solid was filtered off and washed with *n*-pentane, and the amount of neopentane evolved during the grafting reaction was determined by gas chromatography (GC). Dry ethanol was condensed onto the solid, which was then thermally treated at 150 °C. The gas and liquid phases were trapped for GC analysis, and the solid was dried at 100 °C.

The epoxidation reactions were performed in a two-neck flask charged with the metal alkoxide and CH_2Cl_2 . Then DIPT or DET was introduced (usually the natural (+) tartrates; 1.2–1.5 equiv per mol of metal). The flask was cooled to the desired temperature and then the allyl alcohol and a solution of hydroperoxide (cumene hydroperoxide (CHP) or TBHP; 2 equiv per mol of alcohol) were added. The reaction was stopped by removing the catalyst from the solution by filtration. Conversions, yields, and ee values were determined by GC with a chiral γ -cyclodextrin column.

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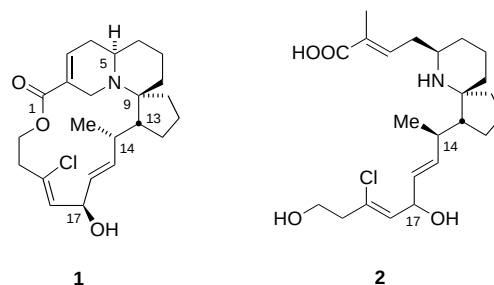
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- [15] This already known surface reaction^[14] leads to the liberation of neopentane (ca. 1.5 mol per mol of grafted Ta) with the formation of a mixture of two well-defined surface species, **2a** and **2b**.
- [16] Step 2: 2.5 mol of neopentane evolved per mol of surface tantalum.
- [17] [Ta]#1: 4.92 wt % Ta, C/Ta = 8.9; [Ta]#2: 5.40 wt % Ta, C/Ta = 7.2; [Ta]#3: 5.63 wt % Ta, C/Ta = 7.1. For a mixture of **3a** (50%) and **3b** (50%) a theoretical value of C/Ta = 7 should be observed; this is the case for [Ta]#2 and [Ta]#3. For [Ta]#1 the higher value may be explained by the presence of SiOEt species.
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Total Synthesis of (+)-Halichlorine: An Inhibitor of VCAM-1 Expression**

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Vascular cell adhesion molecule-1 (VCAM-1), a member of the immunoglobulin superfamily, monitors and regulates leukocyte recruitment into inflamed tissue.^[1] Since leukocyte infiltration is involved in various allergic inflammatory disorders as well as pathogenic processes such as asthma and arteriosclerosis VCAM-1 has emerged as a potential target for drug discovery. In principle, blockade or inhibition of VCAM-1 could have consequences in regulating leukocyte trafficking. Given such considerations an agent that specifically inhibits induced VCAM-1 expression could be of particular interest. While screening for active compounds from marine organisms Uemura and colleagues isolated a substance from the marine sponge *Halichondria okadai* KA-DOTA, which they named halichlorine, and identified its structure as **1**.^[2] A related structure, pinnaic acid (**2**), had been isolated from an Okinawan bivalve *Pinna muricata*.^[3]



Aside from several provocative features of halichlorine, which might pose stimulating opportunities to the organic chemist, this compound commands particular attention because it selectively inhibits the induced expression of VCAM-1 with an IC_{50} of $7 \mu\text{g mL}^{-1}$. Interestingly, pinnaic acid was obtained from a screen designed to identify specific inhibitors of cytosolic phospholipase A_2 (cPLA₂).

Among the challenges posed by halichlorine is that of its total synthesis.^[4] Aside from providing the setting for addressing several interesting chemical issues, its total synthesis holds the prospect of providing probe structures to document structure–activity relationships. Elsewhere we

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