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Diastereoselective Hydroxylation of Titanium Enolates with *tert*-Butylhydroperoxide

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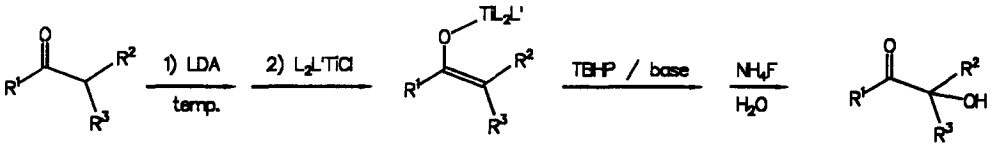
Abstract: The oxidation of titanium enolates with *tert*-butylhydroperoxide has been investigated and the main reaction products, the corresponding α-hydroxyketones **7a-f**, isolated. The highest diastereoselectivities (>95% de) were obtained, when titanium enolates of camphor **2d-6d** were employed. For comparison, the oxidation of the enolates with dimethyldioxirane[1] is discussed.

The transformation of ketones to α-hydroxyketones in a diastereoselective manner is an important method in organic synthesis, and consequently has been investigated by a number of groups. The most common strategy involves the oxidation of enolates with oxidants containing electrophilic oxygen e.g. MoO_5,[2] sulfonyloxaziridines,[3] peracids[4] or dioxiranes.[5] Recently, Adam et al. reported the oxidation of titanium enolates to α-hydroxyketones with dimethyldioxirane (DMD) and found that diastereomeric excesses up to 96% de were achievable.[1] In addition, when the titanium enolate contained a chiral ligand, it was possible to obtain enantiomeric excesses up to 63% ee.[6]

We now wish to report the oxidation of titanium enolates with *tert*-butylhydroperoxide (TBHP). Surprisingly, this reaction does not seem to have been studied despite the fact that the combination $Ti(O^iPr)_4$ / TBHP is an important oxidant in organic chemistry and has been widely used for a number of transformations e. g. for the epoxidation of allylic alcohols (Sharpless epoxidation)[7] and for the oxidation of phenols to quinones or ketols.[8] Recently, the reagent has been used to convert alcohols to carbonyl compounds.[9] For other synthetic use of titanium enolates see .[10]

RESULTS AND DISCUSSION

In the present study the titanium enolates were prepared as described[11] *in situ* from the corresponding lithium enolates, and were then treated with lithium *tert*-butylperoxide ($LiOO^tBu$) or, in comparison with equimolar mixtures of BaO/TBHP or MgO/TBHP or with TBHP. All reactions were carried out between -20° and +25°C. In general the corresponding α-hydroxyketones were isolated as the sole or major product, although in some case side products were observed, generated by aldol condensation (see notes at tables 1 and 2). The resulting products derived from cyclohexanone (**1a**), 2,6-dimethylheptan-4-one (**1b**), isophorone (**1c**), camphor (**1d**), menthone (**1e**) and carvone (**1f**) are presented in table 1.



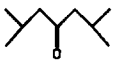
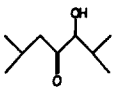
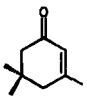
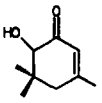
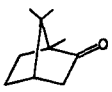
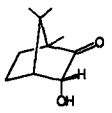
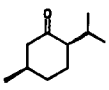
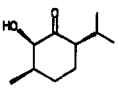
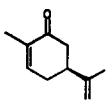
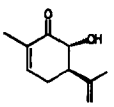
1a - f

2 L= L'=O^{i}Pr
3 L= O^{i}Pr, L'=Cl
4 L= 4-NO_2-C_6H_4-O; L'= Cl
5 L= Cp, L'= Cl
6 L= L'= Cl

7a - f

Scheme 1

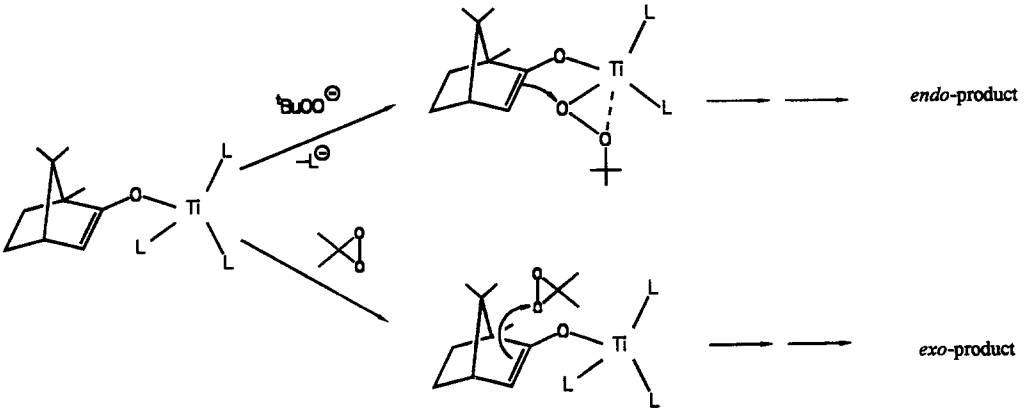
Table 1: Oxidation of Titanium Enolates by TBHP to α-Hydroxyketones

Ketone	L_3Ti	Oxidant (molequiv. to ketone)	Conditions	Products[a]	Conversion[b] (%)	Yield(%) (ref. to conv.)	de[c] (%)
 **1a**	$Ti(O^iPr)_3$	TBHP (1)	Et_2O, -78°C → r.t., 4h	 **7a**	95	53[d]	-
 **1b**	$TiCl(O^iPr)_2$	LiOO^{t}Bu (1)	Et_2O, 0°C, 1.75h	 **7b**	60	40[e]	-
 **1c**	$TiCl(O^iPr)_2$	LiOO^{t}Bu (1)	Et_2O, 0°C, 1.5 h, molecular sieves 4Å	 **7c**	42	>95	-
 **1d**	$TiCl(O^iPr)_2$	LiOO^{t}Bu (1)	THF, 0°C, 1.25 h	 *endo*-7d[f]	50	>95	>95
 **1e**	$TiCl(O^iPr)_2$	BaO/TBHP (1/1)	Et_2O, -20°C, 1.25 h	 *(2R*,3R*,6S*)*-7e[f]	35	>95	60
 **1f**	$TiCl(O^iPr)_2$	MgO/TBHP (1/1)	Et_2O, 0°C, 1.5 h	 *(5S*, 6R*)*-7f[f]	20	>95	40

a) All products were isolated by column chromatography and characterized by GLC MS and ^{1}H NMR spectroscopy. The data for all products were consistent with that from the references cited. b) Conversion refers to ketone introduced determined by GLC and/or ^{1}H NMR. c) de Values were determined directly by ^{1}H NMR analysis of the crude reaction mixture. d) 2-(Cyclohexen-2-yl)-cyclohexanone and 2,6-bis-(cyclohexen2-yl)-cyclohexanone were obtained as aldol side products. e) Aldol side products were detected. f) Major diastereomer is shown.

Remarkably, the oxidation of camphor enolate **3d** led to *endo*-**6d** exclusively (table 1,entry 4) with LiOO^{t}Bu as the oxidizing agent, whereas Adam[1] found that when DMD was used as oxidant *exo*-**6d** (84 % de) was produced. Similarly, the same opposite diastereoselectivity was observed in the oxidation of the titanium enolates derived from menthone (**1e**) i.e. BaO/TBHP (table 1, entry 5) gave mainly the *(2R*, 3R*, 6S*)* diastereomer (60 % de), whilst DMD[1] led mainly to the *(2S*, 3R*, 6S*)* isomer (52 % de).

The difference in the behaviour of the two oxidants (DMD and TBHP) can be explained by the different modes of attack of the oxidants on the titanium enolate. In the case of TBHP, the first step in the reaction involves ligand exchange and the peroxy function becomes activated in a „titanium assisted oxygen-transfer". By contrast DMD does not appear to coordinate with the titanium atom and the TiL_3 group behaves as a bulky substituent in an „outersphere oxygen-transfer" reaction (this is consistent with the behaviour of trimethylsilyl enol ethers, wich give almost the same diastereoisomeric excesses[1]).



Scheme 2

Some remarks should also be made regarding the conversions observed. In general these were found to be < 50 % with the exceptions of cyclohexanone and 2,6-dimethylheptan-4-one (table 1, entry 1 and 2). In these two instances the conversion is high only as a result of aldol side reactions. The use of excess peroxide (up to 500 mol %) did not improve the conversion. Some attempts to optimize the reaction using camphor titanium enolates as model substrates are shown in table 2.

Table 2: Oxidation of Camphor Titanium Enolates **2d - 6d** under various Conditions

Run	L_3Ti	Oxidant (mol equiv. to ketone)	Conditions	Conversion[a] (%)	Yield (%) (ref. to conv.)	de (%)[b]
1	$TiCl(O^iPr)_2$ **(3d)**	LiO^tBu (1)	THF; 0°C; 1.2h	50	>95	>95
2	$TiCl(O^iPr)_2$ **(3d)**	LiO^tBu (1)	THF; 25°C; 1.5h	32	90[c]	69
3	$TiCl(O^iPr)_2$ **(3d)**	LiO^tBu (2)	THF; 0°C; 1.75h	35	>95	>95
4	$TiCl(O^iPr)_2$ **(3d)**	LiO^tBu (1)	Et_2O; 0°C; 1.5h	43	>95	>95
5	$TiCl(O^iPr)_2$ **(3d)**	BaO / TBHP (1/1)	THF; 25°C; 3h	30	>95	>95
6	$TiCl(O^iPr)_2$ **(3d)**	BaO / TBHP (1/1)	Freon 113; 0°C; 2h	30	>95	>95
7	$TiCl(O^iPr)_2$ **(3d)**	MgO / TBHP (1/1)	Et_2O; 0°C; 1.5h	45	>95	>95
8	$TiCl(O^iPr)_2$ **(3d)**	MgO / TBHP (0.5/0.5)	Et_2O; 0°C; 1.5h	30	>95	>95
9	$TiCl(O^iPr)_2$ **(3d)**	KO^tBu (1)	Et_2O; 0 →25°C; 3h	32	>95	>95
10	$Ti(O^iPr)_3$ **(2d)**	TBHP (1)	CH_2Cl_2; -70→25°C; 3.5h	15	>95	82
11	$TiCl(O\text{-}C_6H_4\text{-}4\text{-}NO_2)_2$ **(4d)**	LiO^tBu (1)	THF; 0→25°C; 1.2h	30	>95	95
12	$TiClCp_2$ **(5d)**	LiO^tBu (1)	Et_2O; 25°C; 2.5h	<5	>95	[d]
13	$TiCl_3$ **(6d)**	LiO^tBu (1)	Et_2O; 0→25°C; 20h	56	40[e]	0

a) Conversion refers to camphor introduced. b) Determined directly by ^1H NMR of the crude reaction mixture. c) Aldol condensation product of camphor and 3-hydroxycamphor was obtained (10%) as side product. d) Not determined. e) Main product 3-chlorocamphor (60%, 0% de)

Changing the reaction medium from THF to ether or Freon 113 had little or no effect. Similarly no significant effects were observed when LiOO^{t}Bu was replaced by mixtures of BaO/TBHP or MgO/TBHP or by KOO^{t}Bu. When only TBHP was used, lower de values were obtained even at -70°C (**3d** yielded 50% *endo*-**7d** after treatment with 1 mol equiv. TBHP, -70°C, 6h, 83% de). Varying the ligands at titanium likewise did not lead to any dramatic changes in conversion. Thus (4-$NO_2C_6H_4$-O-)$_2$TiCl and TiCl(O^{i}Pr)$_2$ enolates gave nearly the same results, whilst the Cp_2TiCl enolate (run 12) led to very low conversions. The $TiCl_3$ enolate was not useful at all for the desired transformation, as 3-chlorocamphor had been obtained (run 13). Increasing the reaction temperature from 0° to 25°C led only to a reduction in diastereoselectivity (run 2). This effect was more marked when menthone was employed as the substrate. In that case both higher temperatures or longer reaction times resulted in epimerization not only at C-2 but also at C-6 of the menthone ring with the formation of a mixture of *(2S*, 3R*, 6S*)-*, *(2R*, 3R*, 6S*)-*, *(2S*, 3R*, 6R*)-* and *(2R*, 3R*, 6R*)*-diastereomers of 2-hydroxymenthone.

In summation, a new method for the diastereoselective preparation of α-hydroxyketones from titanium enolates of ketones using commercially available and unexpensive TBHP as oxidant is described, and a mechanism for the oxidation is postulated. Studies to detect a Titanium peroxy bond and the use of chiral ligands at titanium for the enantioselective hydroxylation of prochiral ketones are in progress.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) in $CDCl_3$ solution relative to hexamethyldisiloxane as internal standard. The chemical shifts are reported in ppm (δ scale) relativ to tetramethylsilane. Melting points were recorded on a Boetius Hot stage apparatus. Infrared spectra of thin liquid films between KBr plates were recorded with a Philips FT-IR spectrometer PU 9624.

Typical Procedure: All procedures with the exception of isolation steps were carried out under an atmosphere of nitrogen to exclude atmospheric oxygen and moisture.

In a typical experiment to 5 mmol of the titanium enolate in 10 ml THF, prepared as described[11] from the corresponding lithium enolate and the chloro titanium compound, 5 mmol LiOO^{t}Bu (prepared from 5 mmol TBHP and equimolar amount of 1.6M n-butyllithium in hexane at -78°C) in 10 ml THF were added slowly under vigorous stirring at -20° to 25°C (see tables 1 and 2) over a 1h period. After all peroxide was consumed (detected by TLC, developed with potassium iodide / hydrochloric acid), the reaction mixture was hydrolyzed with 70 ml saturated aqueous NH_4F solution and stirred for additionally 2h. The layers were separated and the aqueous layer was extracted for several times with 10 ml portions of ether. The combined organic phases were dried over $MgCO_3$, the solvent was removed in vacuo (30°C, 20 torr) and the products were isolated.

2-Hydroxycyclohexanone (7a): Using the above procedure with titanium enolate **2a** as substrate, the crude reaction mixture was analyzed directly. No isolation was carried out. The reaction products were characterized by GLC and GLC MS using standards prepared by known procedures.[12]

3-Hydroxy-2,6-dimethylheptan-4-one (7b): Using the above procedure with titanium enolate **3b** as substrate the crude mixture of products was obtained. **7b** was isolated as colorless liquid by column chromatography (silica gel 40, hexane / EtOAc / CH_2Cl_2 8:1:1). ^{1}H NMR: 0.69 ppm (d, J=6.71 Hz, 3H, CHOH-CH(CH_3)CH_3); 0.92 ppm (d, J=6.71 Hz, 3H, $CH_2CH(CH_3)_2$), 0.93 ppm (d, J=6.87 Hz, 3H, $CH_2CH(CH_3)_2$); 1.10 ppm (d, 5.86 Hz, 3H, CHOH-CH(CH_3)CH_3); 2.1-2.25 ppm (m, 2H, $CH(CH_3)_2$); 2.26-2.36 ppm (m, 2H, CH_2); 3.35 ppm (very broad, 1H, OH); 3.99 ppm (d, J=2.49 Hz, 1H, CHOH); GLC MS: (EI) m/z: 159 ([M+H]$^+$, 100); 85 (18); 73 (35); IR : 1722 cm^{-1} (C=O).

6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (7c): Using the above procedure with the titanium enolate **3c**, the crude product 7c was purified by column chromatography (silica gel RP-18, H_2O / MeCN / THF 8:5:1). The spectroscopic data are in accord with the literature data.[4]

3-Hydroxy-1,7,7-trimethyl[2.2.1]bicycloheptan-2-one (7d): The crude products obtained by the above procedure using titanium enolates **2d - 6d** were purified by column chromatography (silica gel 40, ether / hexane 1:1). After purification no separation of the *endo-* and *exo*-isomers was achieved. The de values were determined by ^{1}H NMR spectroscopy integrating the signals at δ=4.21 ppm (*endo*-isomer) and δ=3.70 ppm (*exo*-isomer).
Melting points: **7d** (60 % de): 184°C (Lit[2]: (67% de) 170-183°C); **7d** (~100 % de): 195-198°C (Lit.[2]: (*endo*-**7d**):192-195°C) The NMR data are in accord with the published data.[2]

2-Hydroxy-3-methyl-6-isopropylcyclohexanone (7e): A mixture of crude products was obtained using the above procedure with titanium enolate **2e** and **3e** and was purified by column chromatography (silica gel 40, ether / hexane 1:1). The spectroscopic data were in accord with the published data.[1] The de values were determined by ^{1}H NMR spectroscopy integrating the signals at δ=3.63 ppm *(2R*, 3R*, 6S*)*-**7e** and δ=4.35 ppm *(2S*, 3R*, 6S*)*-**7e**.

6-Hydroxy-5-isopropenyl-2-methyl-2-cyclohexen-1-one (7f): The crude products were obtained by following the above procedure using titanium enolate **3f**. The title compound *(6R*, 5S*)*-**7f** and the minor isomer *(6S*, 5S*)*-**7f** were separated by column chromatography (silica gel 40, cyclohexane / EtOAc / CH_2Cl_2 8:2:1). Both products were isolated as oils. Spectroscopic data of *(6R*, 5S*)*-**7f** are consistent with the published data.[13] *(6S*, 5S*)*-**7f**: ^{1}H NMR : 1.67 ppm (s, 3H, ^{i}propylidene-**CH**$_3$); 1.81 ppm (d, J = 1 Hz, 3H, **CH**$_3$); 2.51 ppm (dm, J_1 = 19.4 Hz, J_2 = 2.7 Hz, 1H, **H**CH-axial); 2.71 ppm (dm, J_1 = 19.4 Hz, J_2 = 2.8 Hz, 1H, HC**H**-equ.); 3.16 ppm (m, 1H, C**H**C(CH$_2$)(CH$_3$)); 3.58 ppm (br. s, 1H, O**H**); 4.4 ppm (d, J = 5.8 Hz, 1H, C**H**OH); 4.69 ppm (s, 1H, =C**H**$_2$); 4.84 ppm s, 1H, =C**H**$_2$); 6.65 ppm (s, 1H, =C**H**-). GLC MS: (EI) m/z: 167 ([M+H]$^+$, 25); 148 (25); 138 (40); 109 (35); 82 (100) IR : 1674 cm^{-1} (C=O).

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