

# Diastereoselective epoxidation of hydroxy-containing unsaturated terpenes on heterogeneous titanium-catalyst

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## Abstract

The diastereoselective epoxidation of substrates of interest as fine chemicals is here reported and the role of the OH-function in this reaction was studied particularly on non-allylic unsaturated terpenes. A heterogeneous system obtained grafting a titanocene precursor onto a commercial silica was used as catalyst. © 2002 Elsevier Science B.V. All rights reserved.

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## 1. Introduction

One of the most attractive targets for chemistry in these last years is selective synthesis, which reduces the amount of substrate per unit of product as well as the production of wastes. Stereoselective transformations are particularly relevant for the production of fine and speciality chemicals.

In this aim, the search for an efficient stereoselective catalytic system for the epoxidation in heterogeneous phase is an attractive task in chemical synthesis. Such a system should join the main features of two classes of catalysts: the high selectivity, the wide versatility and synthetic potential of homogeneous epoxidation catalysts and the ease in separation and recycling, which is typical of heterogeneous solid catalysts.

Up to now, among heterogeneous epoxidation catalysts, titanium-containing silicates have shown the best activity and selectivity results [1]. Nevertheless,

even though many authors dealt with diastereoselective epoxidation on homogeneous catalysts [2], there are only few studies about the diastereoselective performances of heterogeneous systems on substrates of interest in fine chemistry processes [3–9]. Further, in most works regarding titanium-containing silicates, the stereoselectivity was studied mainly on allylic alcohols [1].

Taking into account the catalyst preparation, the use of a titanium-catalyst supported on commercial silica materials could allow a wider exploitation of these heterogeneous systems. In fact, some interesting attempts have been recently reported in the anchoring of titanium precursors on silica in order to avoid the strict synthesis conditions and the expensive preparation procedures of structured porous titanosilicates [10–12]. Some of these catalytic systems have also been employed in the oxidation of fine chemicals with *tert*-butylhydroperoxide (TBHP) [13].

Here we wish to report the high stereoselectivity obtained in the epoxidation of molecules of interest in the flavour and fragrance industry on catalysts which are not only heterogeneous, but also more

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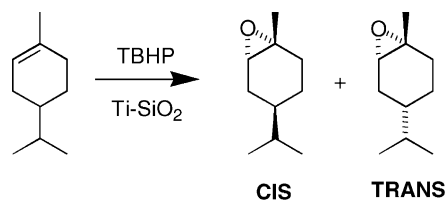
easily prepared than other microporous or mesoporous titanium-containing silicates [14].

## 2. Experimental

A titanium-containing porous silica (Ti-SiO<sub>2</sub>) was used as heterogeneous catalyst. SiO<sub>2</sub> Grace Davison 62 (2.00 g; mean pore diameter and specific surface area, 14 nm and 357 m<sup>2</sup> g<sup>-1</sup>, respectively) was thoroughly washed with 1 M HNO<sub>3</sub>, rinsed with distilled water and dried overnight at 423 K in air. Before anchoring, it was heated in air at 773 K for 1 h and then in vacuo at the same temperature for 6 h. Titanocene dichloride (188 mg; Fluka, Purum) was dissolved in 60 ml of anhydrous CHCl<sub>3</sub> (Prolabo, RP) under argon. The resulting solution was added to the dried SiO<sub>2</sub> and stirred for 30 min at room temperature. Freshly distilled triethylamine (1.00 ml; Carlo Erba, RPE) was then added to the suspension and left under stirring overnight. The solid was filtered on a Büchner funnel, washed with fresh CHCl<sub>3</sub> and dried for 3 h. It was calcined at 823 K in flowing oxygen (80 ml min<sup>-1</sup>) for 6 h. Owing to the grafting technique, all the titanium sites should virtually be exposed and active in the epoxidation reaction. The resulting solid contains 1.75 wt.% Ti (determined by ICP–AES).

The terpenes **1–3**, **5** and **6** were used as received (Aldrich). Menth-1-ene **4** was prepared from limonene **5** by hydrogenation with Rh[(PPh<sub>3</sub>)<sub>3</sub>]Cl [15]. The epoxidation tests on the terpenes were carried out in a glass batch reactor at 358 K using acetonitrile (Aldrich, HPLC grade) and ethylacetate (AcOEt; Carlo Erba, RPE), as solvents, previously dried on molecular sieves (Siliporite A). Anhydrous TBHP (Aldrich, 5 M solution in decane) was used as oxidant (oxidant:substrate molar ratio = 1.1) and the catalyst to substrate ratio was 30 wt.%. Samples were taken after a reaction time of 1 and 24 h and the catalytic performances were computed on GC chromatograms (HP5890; DB-225 column, 30 m × 0.25 mm; FID and MS detectors). Mesitylene was used as internal standard. The *cis:trans* ratios were determined by <sup>1</sup>H-NMR analysis (Bruker DRX 300) of the 24 h reaction mixture, after solvent removal in vacuo.

In the tests for checking the leaching of catalytically active titanium species, the reaction mixture was stopped at ca. 40% conversion (2 h reaction) and



Scheme 1.

centrifuged under inert atmosphere. The resulting clear and colourless solution was tested for further reaction under the same conditions used above in the following 22 h with no solid catalyst. In these tests a higher amount of organic hydroperoxide was used (TBHP:terpene molar ratio = 1.5) to ensure an oxidant excess.

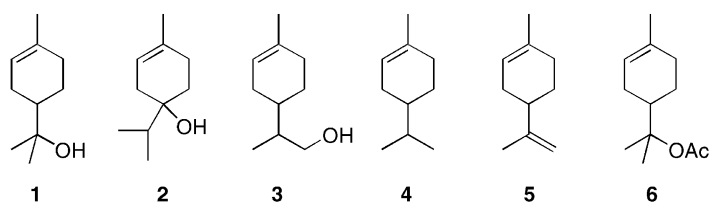
In the tests for the recovery of the catalyst, the solid was separated by filtration on Büchner funnel, thoroughly washed with fresh solvent, activated again at 773 K in air and then reused in another test as described above. Naming of *cis-trans* diastereoisomers is based on the positions of the C-1 methyl and C-4 isopropyl substituents with respect to the six-membered cyclohexene ring (Scheme 1).

## 3. Results and discussion

In this work the methodology by Thomas and co-workers [16] of preparing highly active titanasilicate catalysts from a titanocene precursor has been successfully applied onto a commercial porous silica.

The hydroxy-directed diastereoselective epoxidation was studied on a series of non-allylic terpenic unsaturated compounds, i.e.  $\alpha$ -terpineol (**1**), terpinen-4-ol (**2**), menth-1-en-9-ol (**3**), menth-1-ene (**4**), limonene (**5**) and  $\alpha$ -terpinylacetate (**6**) (Scheme 2). The results recorded in the epoxidation of the terpenes on Ti-SiO<sub>2</sub> are listed in Table 1.

It is worthwhile noting that with alcoholic terpenes (substrates **1**, **2** and **3**) a higher conversion is obtained whenever the reaction is run in ethylacetate instead of in acetonitrile. However, the epoxide selectivity values are worse in the former solvent than in the latter. Since in ethylacetate a higher amount of acid-catalysed by-products was detected, this behaviour is likely due to the lower basic character of this solvent with



Scheme 2.

respect to acetonitrile, as already noted elsewhere on mesostructured titanosilicates [17]. On the other hand, with non-alcoholic terpenes **4**, **5** and **6** the differences in specific activity between the two solvents are not so large, because non-alcoholic epoxides are less prone to intramolecular acid-catalysed side reactions than alcoholic ones.

Regarding the diastereoselectivity with **1** and **2**, in both solvents, only one of the two possible diastereoisomers is detected by NMR spectroscopy. On the contrary, on **3** the formation of the *trans* isomer alone is observed only in ethylacetate; in acetonitrile a small amount of *cis* isomer is also obtained.

Whenever OH-group is absent, as in **4** and **5**, or replaced by an acetyl group, as in **6**, a diastereospecific

behaviour was not observed in either solvent and the diastereoisomeric excess values decreased abruptly. Anyway, a global trend towards the formation of *trans* isomer passing from acetonitrile to ethylacetate is noted (substrates **3** through **6**).

From these data it is evident that the OH-moiety plays a key role in directing the diastereospecific epoxidation of bulky unsaturated terpenes and the oxygen transfer from TBHP to double bond occurs on the same side of the rigid six-membered ring where the hydroxy-group is placed. The high selectivity observed on these OH-bearing substrates is consistent with the control of diastereoselectivity through the conformational strain and hydrogen bonding observed on allylic substrates [18]. Thanks to the inherent

Table 1

Epoxidation of the unsaturated terpenes **1–6** on Ti-SiO<sub>2</sub> (reaction conditions: 30 wt.% catalyst; TBHP:terpene molar ratio = 1.1; 358 K; 24 h)

Substrate	Solvent	Conversion (%) <sup>a</sup>	Selectivity (%) <sup>b</sup>	TOF (h <sup>-1</sup> ) <sup>c</sup>	<i>cis:trans</i> ratio <sup>d</sup>
<b>1</b>	CH <sub>3</sub> CN	66	56	8.0	0 <sup>e</sup> :100
<b>1</b>	AcOEt	78	48	9.7	0 <sup>e</sup> :100
<b>2</b>	CH <sub>3</sub> CN	70	80	14.7	100:0 <sup>e</sup>
<b>2</b>	AcOEt	85	50	29.6	100:0 <sup>e</sup>
<b>3</b>	CH <sub>3</sub> CN	72	63	15.9	9:91
<b>3</b>	AcOEt	93	48	23.7	0 <sup>e</sup> :100
<b>4</b>	CH <sub>3</sub> CN	90	87	28.8	12:88
<b>4</b>	AcOEt	85	71	19.9	11:89
<b>5</b>	CH <sub>3</sub> CN	57	89 <sup>f</sup>	13.3	44:56
<b>5</b>	AcOEt	61	74 <sup>g</sup>	11.4	22:78
<b>6</b>	CH <sub>3</sub> CN	83	84	25.4	17:83
<b>6</b>	AcOEt	80	84	27.1	5:95

<sup>a</sup> Conversion after 24 h, as determined by GC analysis ( $\pm 2\%$ ) based on alkene consumption.

<sup>b</sup> Selectivity to 1,2-epoxides after 24 h.

<sup>c</sup> Turnover frequency after 1 h.

<sup>d</sup> Determined by <sup>1</sup>H-NMR analysis ( $\pm 5\%$ ) of the crude product mixture after 24 h.

<sup>e</sup> Under detection limit.

<sup>f</sup> Endocyclic:exocyclic epoxide selectivity ratio = 82:18.

<sup>g</sup> Endocyclic:exocyclic epoxide selectivity ratio = 80:20.

rigidity of cyclic systems, such a control applies, in this case, also to compounds in which the alcoholic group is placed far from the unsaturation (substrates **1**, **2** and **3**).

Comparing  $\alpha$ -terpineol **1** and  $\alpha$ -terpinylacetate **6**, the main difference being the ability in interacting through hydrogen bonds, it is evident that the presence of OH-group, even in bishomoallylic position, is responsible for the specific formation of the *trans*-epoxide alone (cf. *cis:trans* ratios of **1** and **6** in both solvents). On **3**, instead, the alcoholic function is far enough from sterical hindrances and is able to point more freely on both sides of the cyclohexene ring. In this case, the OH-group in **3** has a higher conformational freedom than in **1**. This may account for the small amount of *cis*-epoxide formation and for the lower diastereoselectivity observed in the epoxidation of **3** in acetonitrile.

On all the substrates ethylacetate is more effective in directing the  $\pi$ -facial attack than acetonitrile and higher diastereoisomeric excess values were recorded in the former than in the latter solvent. The role of the solvent in the epoxidation of cyclic unsaturated alcohols with homogeneous catalyst has already been highlighted [19–21]. Anyway, on such heterogeneous systems, further tests with different solvents are needed in order to evaluate the parameters influencing the diastereoselective behaviour.

For some redox solid catalysts are not stable towards leaching under oxidising conditions in liquid phase,

it is necessary to perform specific tests to determine whether the system is or is not really heterogeneous [22].

So, to check whether there is a valuable leaching of catalytically active titanium species in homogeneous phase, in some epoxidation tests of **1** the solid catalyst was removed from the liquid mixture by centrifugation and the resulting solution was tested for further reaction. Figs. 1 and 2 show the data obtained in the tests after Ti-SiO<sub>2</sub> removal.

It is evident that, under these conditions, in both solvents no further oxidation activity was noted. Indeed, even though a progress in alkene conversion was observed in the 22 h after solid catalyst removal (ca. 13 and 6% in CH<sub>3</sub>CN and AcOEt, respectively), in neither case there was a rise in the amount of  $\alpha$ -terpineol epoxide. Rather, the tiny consumption of substrate and epoxide should be ascribed to secondary non-oxidative reaction, as confirmed by gas-chromatographic analysis. These data mean that, even if there is a leaching of titanium species in the reaction solution (it is likely when OH-containing substrates are produced as side products [23]), such metallic compounds do not act as homogeneous catalyst under these conditions.

The catalytic performances of Ti-SiO<sub>2</sub> in the second run of epoxidation of  $\alpha$ -terpineol **1** are listed in Table 2. In these tests Ti-SiO<sub>2</sub>, after the first run, was filtered and calcined at 773 K in air to remove organic adsorbates from the catalyst surface. It is worth noting that the *trans* selectivity was again the same in the

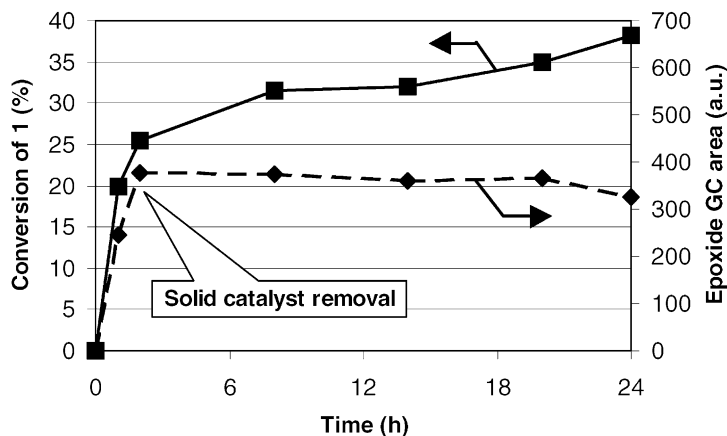


Fig. 1. Alkene conversion (■) and epoxide production (◆) in the epoxidation of  $\alpha$ -terpineol **1** in acetonitrile. Reaction of the liquid mixture after Ti-SiO<sub>2</sub> removal. Conditions: TBHP:terpene molar ratio = 1.5; 358 K.

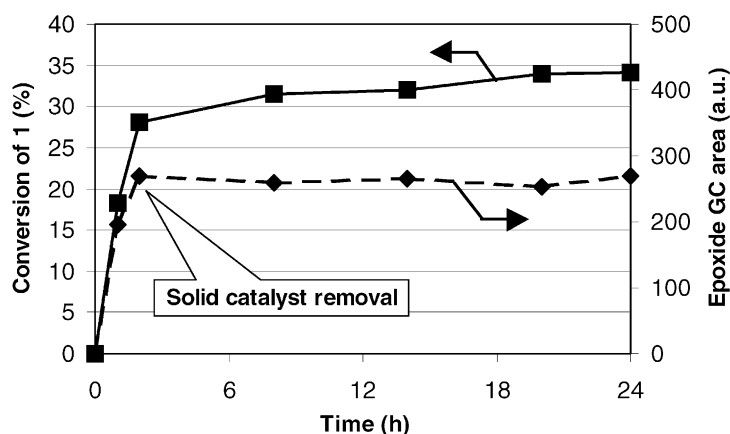


Fig. 2. Alkene conversion (■) and epoxide production (◆) in the epoxidation of  $\alpha$ -terpineol **1** in ethylacetate. Reaction of the liquid mixture after Ti-SiO<sub>2</sub> removal. Conditions: TBHP:terpene molar ratio = 1.5; 358 K.

Table 2

Epoxidation of  $\alpha$ -terpineol **1** on Ti-SiO<sub>2</sub> (second run after filtration and calcination of the solid catalyst at 773 K in air, reaction conditions: recovered catalyst; TBHP:terpene molar ratio = 1.1; 358 K; 24 h)

Solvent	Selectivity (%) <sup>a</sup>	TOF (h <sup>-1</sup> ) <sup>b</sup>	<i>cis:trans</i> ratio <sup>c</sup>
CH <sub>3</sub> CN	58	8.3	0 <sup>d</sup> :100
AcOEt	51	4.1	0 <sup>d</sup> :100

<sup>a</sup> Selectivity to 1,2-epoxides.

<sup>b</sup> Turnover frequency after 1 h.

<sup>c</sup> Determined by <sup>1</sup>H-NMR analysis ( $\pm 5\%$ ) of the crude product mixture.

<sup>d</sup> Under detection limit.

second run in both solvents. On the other hand, while the recycling tests carried out in acetonitrile gave practically the same activity and selectivity values as in the first run, in ethylacetate an abrupt loss (about 55% less) of specific activity was registered.

Further study is needed to ascertain whether the different features of the two solvents (e.g., the basic or the polar character) could account for the different stability of Ti-SiO<sub>2</sub> towards recycling.

#### 4. Conclusions

A heterogeneous epoxidation catalyst was prepared grafting titanocene dichloride onto a commercial amorphous silica and it was tested in the epoxidation

of a series of OH-containing non-allylic unsaturated terpenes. Complete diastereoselectivity was obtained on homoallylic and bishomoallylic substrates **1** and **2** and the role of the hydroxy-group in directing the diastereospecific epoxidation was hence highlighted. With regard to the influence of the solvent on the diastereoselectivity, the reactions run in ethylacetate showed higher diastereoisomeric excess values than those in acetonitrile.

The development of well-defined catalytic species onto suitable supports obtained by anchoring or tethering techniques may represent a link between the high performances of molecular homogeneous catalysts and the practical advantages of heterogeneous solid catalysts.

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